PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 471/18, 471/22, 515/18, 498/18, 513/18, A61K 31/47

A1

(11) International Publication Number: WO 97/48705

(43) International Publication Date: 24 December 1997 (24.12.97)

(21) International Application Number: PCT/GB97/01659

(22) International Filing Date: 19 June 1997 (19.06.97)

(30) Priority Data:
9612829.3 19 June 1996 (19.06.96) GB

(71) Applicant *(for all designated States except US)*: UNIVERSITY COLLEGE LONDON [GB/GB]; Gower Street, London WC1E 6BT (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CAMPOS-ROSA, Joaquin [ES/ES]; Avenida de Cervantes, 10, 7° D, E-18008 Granada (ES). DUNN, Philip, Michael [GB/GB]; 133 Knaves Hill, Linslade, Leighton Buzzard, Bedfordshire LU7 7SL (GB). GALANAKIS, Dimitrios [GR/GR]; 12 Olympou, 751 Panorama, GR-552 36 Thessaloniki (GR). GANELLIN, Charon, Robin [GB/GB]; Kinwood, Briary Wood End, Welwyn, Hertfordshire AL6 0TD (GB). JENKINSON, Donald, Hugh [IE/GB]; 35 Wood Vale, Muswell Hill, London N10 3DJ (GB). YANG, Donglai [CN/GB]; 49 Linthorpe Road, London N16 5QT (GB). CHEN, Jianqing [CN/CA]; 213 Strathmore Boulevard, Toronto, Ontario M4J 1P4 (CA).

(74) Agents: PAGET, Hugh, C., E. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).

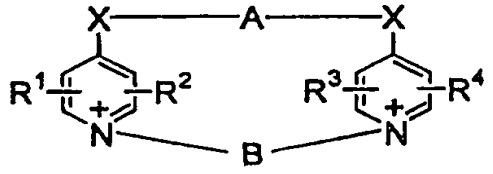
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

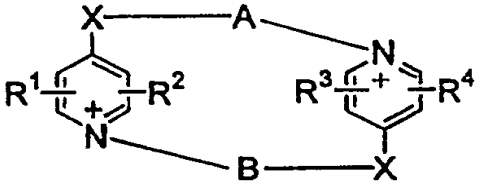
(54) Title: POTASSIUM CHANNEL BLOCKERS

(57) Abstract

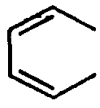
A series of compounds for blocking calcium activated potassium channels in rat sympathetic neurones and other mammalian cells, and a method for producing them. These compounds with general formulae (I) and (II), where A and B are spacing groups of 3 to 15 carbon atoms Q^- is the conjugate base of an acid, R^1 and R^4 are for example (a), R^2 and R^3 are for example H, and X is for example NH, exhibit a high potency and are expected to show selectivity between different channel types. The compounds may be useful in the treatment of a number of disorders that are associated with the activity of calcium activated potassium channels, e.g. myotonic muscular dystrophy, gastrointestinal dysmotilities, memory disorders, cancers, narcolepsy and ethanol-induced narcosis. The compounds may also be useful as antibacterial agents.



(I)



(II)



(a)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

POTASSIUM CHANNEL BLOCKERS

TECHNICAL FIELD

The present invention relates to compounds having pharmaceutical (including veterinary) use, in particular compounds capable of blocking calcium activated potassium channels in human and other mammalian cells, to methods of making such compounds and to the use of such compounds in the treatment of various disorders.

BACKGROUND OF THE INVENTION

Ca^{2+}-activated K^+ channels are found in a wide variety of cell types and can be divided into three main classes on the basis of single channel conductance and sensitivity to blocking agents. Of these, the SK_{Ca} channel is characterized by its small single channel conductance (6-20 pS) and high sensitivity to the bee venom toxin apamin. Estimates of the apamin concentration required to cause 50% block of SK_{Ca} channels vary considerably between cells, ranging from 0.2 to 20 nM. Also, the action of apamin may reverse rapidly or very slowly, depending on the cell type. From these observations it might be inferred that

subtypes of SK_{Ca} channels exist.

In recent work by a group including some of the present inventors [British Journal of Pharmacology (1996) 117, 35-42] it has been found that a bis-quaternary quinolinium compound, 8,19-diaza-3,5(1,4)-dibenzena-1,7(1,4)-diquinolina-cyclononadecaphane referred to below as Compound A, exhibits the ability to block the SK_{Ca} channel in rat sympathetic neurones and guinea-pig hepatocytes. This compound was compared with gallamine and dequalinium; a large difference in the relative potency of these compounds was found between the two tissues providing strong functional evidence for SK_{Ca} channel heterogeneity.

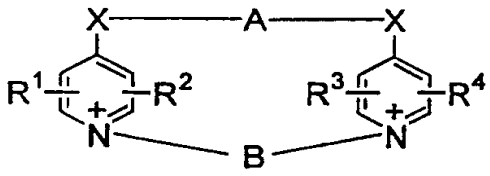
DISCLOSURE OF THE INVENTION

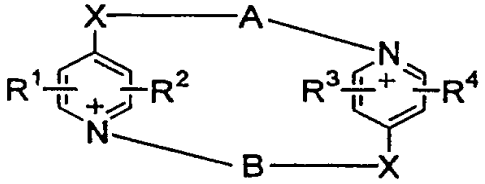
An aim of the present invention is to provide compounds suitable for blocking SK_{Ca} channels that are not peptides and are more potent than known compounds.

A further aim of the present invention is to provide compounds that exhibit selectivity in blocking SK_{Ca} channels in different cells.

A first aspect of the present invention provides a

compound having the general formula I or II:

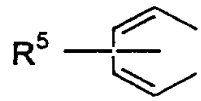




or any one of its conjugate bases

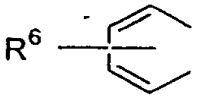
where:

each Q^- is the conjugate base of a pharmaceutically acceptable inorganic or organic acid;

R^1 is selected from H and 

R^5 being selected from H, and substituents such as a halogen, an alkyl group with 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an amino group, an alkylamino group, a hydroxy group and an alkoxy group;

R^2 and R^3 are independently selected from H, and substituents such as a halogen, an alkyl group with 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an amino group, an alkylamino group, a hydroxy group and an alkoxy group;

R^4 is selected from H and 

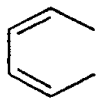
R^6 being selected from H, and substituents such as a halogen, an alkyl group with 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an amino group, an alkylamino group, a hydroxy group and an alkoxy group;

where R^2, R^3, R^5 and R^6 may be present once or a plural number of times on the respective rings;

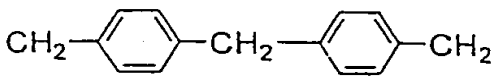
each X is independently selected from NH, NR^7, O, S and CH_2, R^7 being selected from alkyl, aryl, alkaryl and aralkyl groups having 1 to 10 carbon atoms;

A and B which are the same or different, are each selected from a spacing group with a chain length of 3 to 15 atoms;

except that in general formula I when

R^1 and R^4 are 

R^2 and R^3 are H, X is NH, and A is $(CH_2)_{10}$,

B cannot be  .

The term "chain length" throughout this description and

claims should be taken to mean the lowest number of atoms between one end of the spacing group and another. The spacing group may contain rings, e.g. cycloalkyl and aromatic, including heterocyclic, substituted or unsubstituted. The spacing groups may contain one or more O or S atoms as part of the chains. The type of linkages possible with these atoms are for example an ether linkage (-O-),and thio linkages (-S-) and (-S-S-). To avoid instability these linkages should not be adjacent to the N atoms of the pyridine or quinoline rings or to X if X is NH, O or S. Aditionally it is preferable that no methylene group has a hetero atom on both sides.

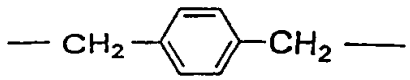
Examples of the spacing groups A and B are given below. The preferred chain length is 3 to 10, more preferably 4 to 7.

It is preferred that X is NH, R^1 and R^4 are  and R^2 and R^3 are H.

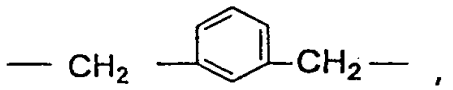
When any of R^2,R^3,R^5 and R^6 are not H, it may be any substituent which is pharmaceutically acceptable and which does not remove the potency of the molecule in the effects described herein, in particular the blocking of Ca^{2+}-activated K^+ channels. Some suitable substituents are given above. Others are such as acyl, -CH, etc.

Compounds which have shown greater potency for blocking SK_{Ca} channels are where A is selected from

$-(CH_2)_n-$, where n=3-6,



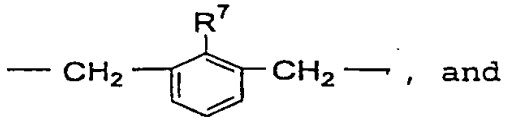
and



and B is selected from

$-(CH_2)_n-$ where n=4-6,

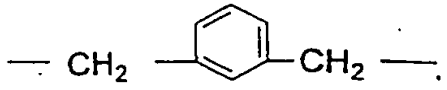
and



R^7 is selected from H, OH, OMe.

The two most potent compounds are where both A and B are $-(CH_2)_5-$ and where A is

and B is

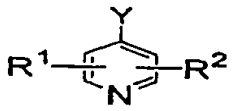


These spacing groups have a chain length of 5 and 6 respectively.

Without being bound by theory, it can be supposed that the compounds of the present invention work as potassium channel blockers by the virtue that they exhibit the property of a relatively determined spatial relationship between the two pyridine or quinoline rings of the compound; the two spacing groups hold the two pyridine or quinoline rings in this spatial relationship. This relationship may not be obtained when only one spacing group is present between the two pyridine or quinoline rings since the conformation of the spacing group changes. It appears to the present inventors that the chain length between the two pyridine or quinoline rings affects the potency of the compound as a SK_{ca} channel blocker. For these reasons, it is at present believed that the function of the spacing groups is primarily to provide a stable linkage between the two pyridine or quinoline rings, the chemical nature of these spacing groups being preferably relatively inert.

In the compounds of the invention, the substituent groups such as alkyl, alkylamono, alkoxy, aryl, aralkyl and alkaryl mentioned above may be optionally substituted by substituents which do not remove the desired effect of the compound.

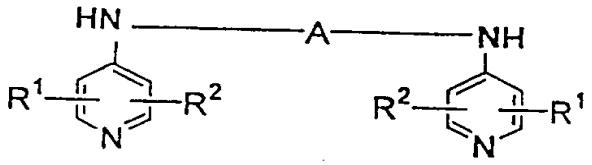
A second aspect of the present invention provides a method for producing a compound of the invention as described above having the general formula I, by reacting a compound of the general formula:



with a compound of the formula

$$H_2N - A - NH_2$$

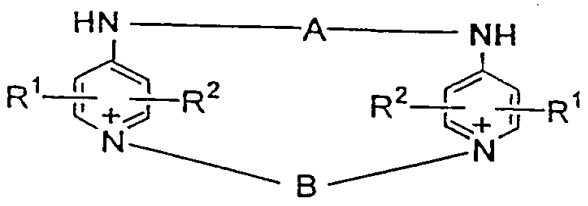
to give



which is then further reacted with a compound of the formula

$$Z - B - Z$$

to give

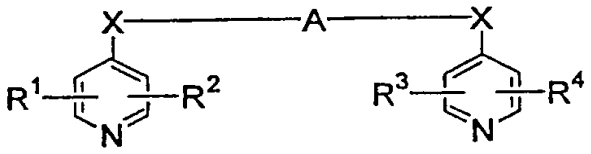


or any one of its conjugate bases,

where

Y and Z are independently selected from a sulphonate, Cl, Br and I.

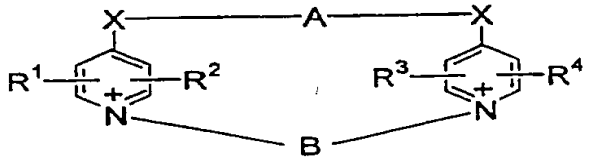
There is further provided a method for producing a compound of the invention as described above having the general formula I, by reacting a compound of the general formula



with a compound of the general formula

Z - B - Z

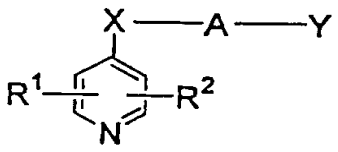
to give



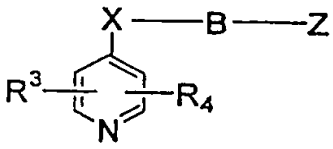
I

where Z is selected from Cl, Br and I.

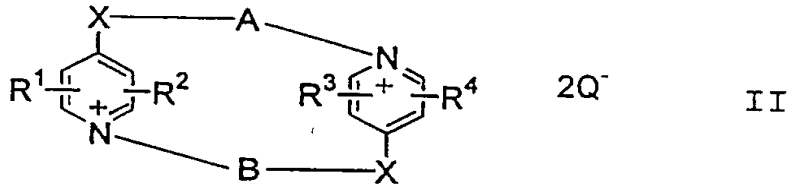
In yet another aspect of the invention there is provided a method for producing a compound of the invention as described above having the general formula II, by reacting a compound of the general formula III



with a compound of the general formula IV



to give



II

where Y and Z are independently selected from Cl, Br and I.

In this method Compounds III and IV may be identical.

Pharmaceutically acceptable acids as mentioned in the above two aspects are exemplified by hydrochloric, hydrobromic, boric, phosphoric, sulphuric, acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, trifluoroacetic and glucose-1-phosphoric acids.

A third aspect of the present invention provides the use of compounds of the present invention in the treatment of any one of the following disorders: myotonic muscular dystrophy, gastrointestinal dysmotilities, disorders of memory, narcolepsy and associated disorders, cancers, ethanol-induced neurotoxicity and bacterial infection.

A fourth aspect of the present invention provides the use of compounds of the present invention in the preparation of a pharmaceutical for the treatment of any one of the following disorders: myotonic muscular dystrophy, gastrointestinal dysmotilities, disorders of memory, narcolepsy and associated disorders, cancers, ethanol-induced neurotoxicity and bacterial infection.

A fifth aspect of the present invention provides a pharmaceutical composition containing a compound of the present invention.

In accordance with the present invention, compositions provided may be administered to human individuals or used as a veterinary medicine, particularly for other mammals. Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit

may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, eg decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors.

Pharmaceutical compositions according to the present invention, and for use in accordance with the present invention, may comprise, in addition to active ingredient, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g. cutaneous, subcutaneous or intravenous.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil.

Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, tonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

EXAMPLES

Embodiments of the invention will now be given in detail by way of example. We describe syntheses of compounds of the invention, identified as Compound 1 etc., and of intermediates and starting materials.

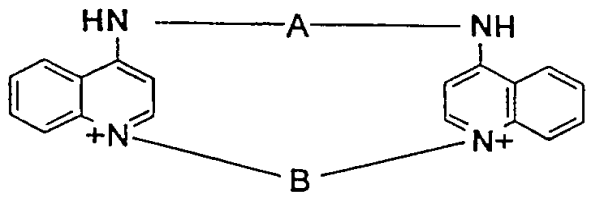
In the following syntheses of compounds 1 to 41, where preparative high performance liquid chromatography

(HPLC) was performed, it was carried out with a Gilson apparatus using a UV detector and a Kromasil C18 5 μm column. Solvent mixtures of water + 0.1% trifluoroacetic acid (TFA) and MeOH + 0.1% TFA were used with a flow rate of 20 ml/min. In many cases, some excess TFA is retained in the salts after HPLC, as well as CH_3OH and H_2O.

mp is melting point, but where this is followed by (dec) or (decomp), it indicates decomposition at the temperature given. bp is boiling point.

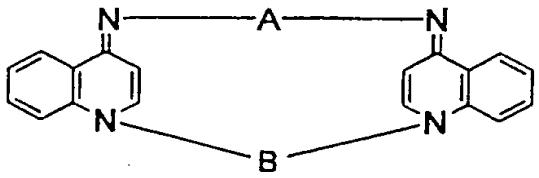
MeOH is CH_3OH, EtOH is C_2H_5OH, DMF is dimethyl formamide.

The structures of the Compounds 1 to 41 of the invention can all be represented by the general formula:



$2Q^-$

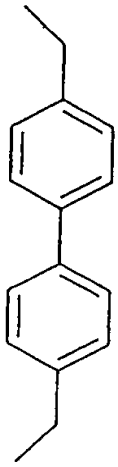
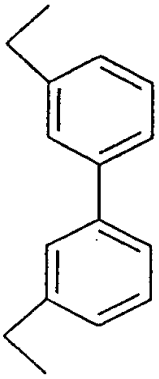
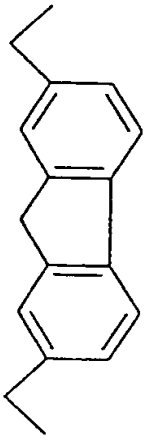
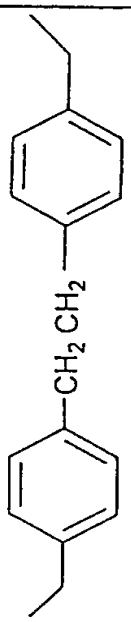
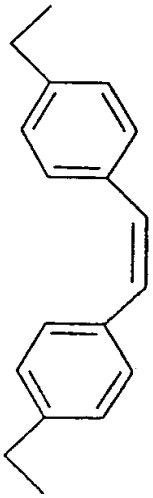
An alternative structural representation is:

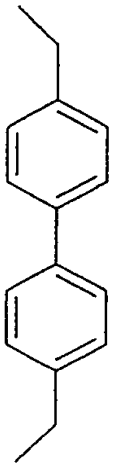
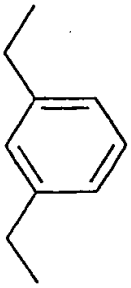
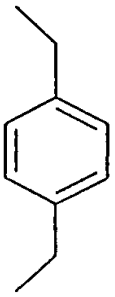
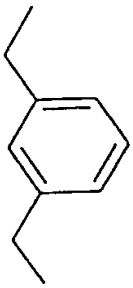
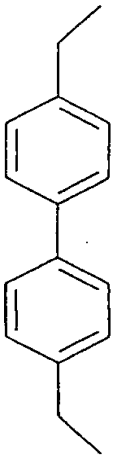
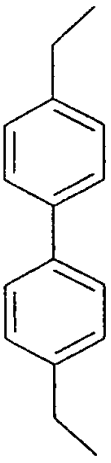
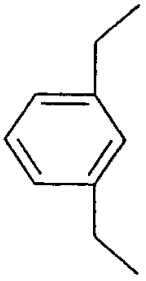
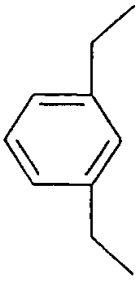
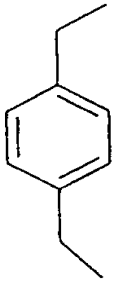


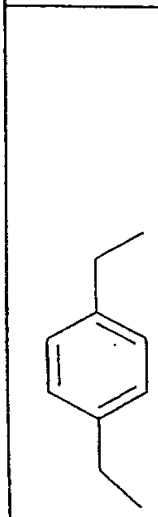
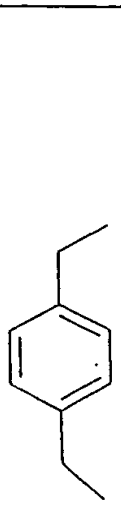
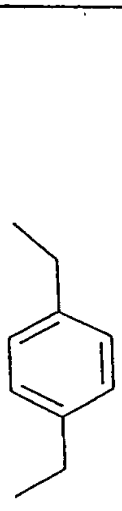
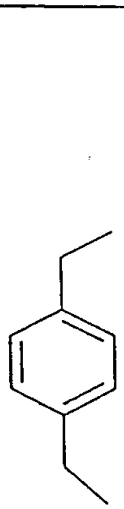
which illustrates the conjugate base.

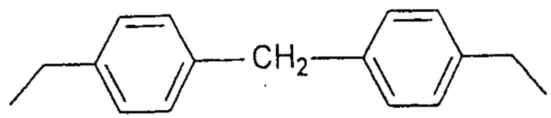
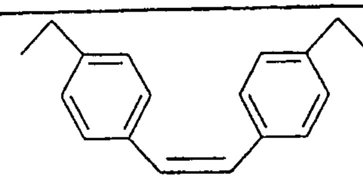
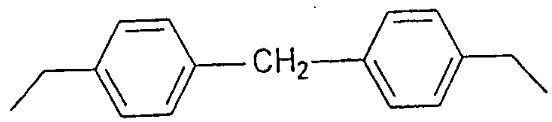
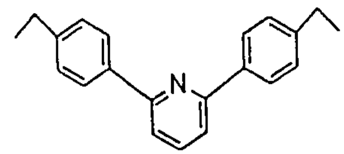
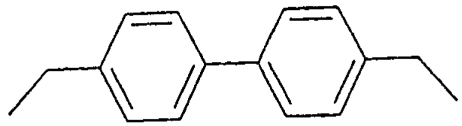
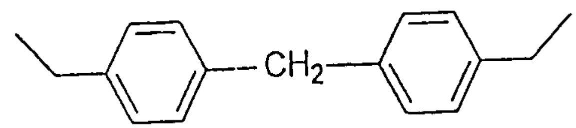
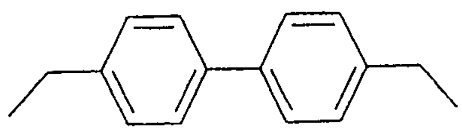
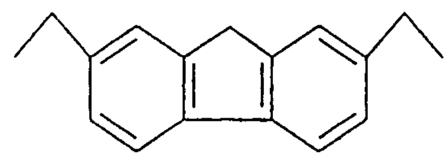
Groups A and B are detailed in Table 1 for each of Compounds 1 to 41.

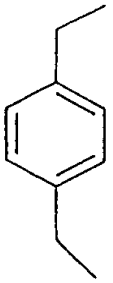
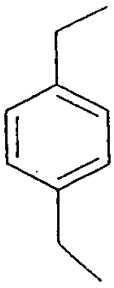
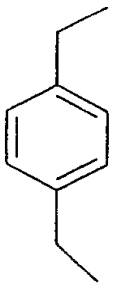
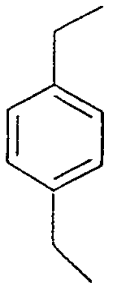
Table 1

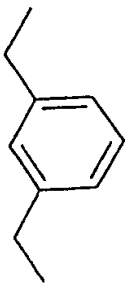
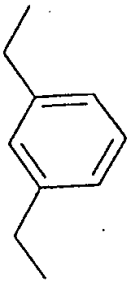
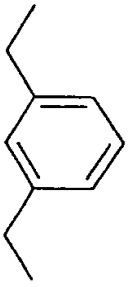
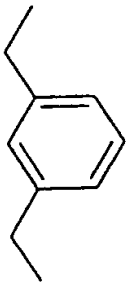
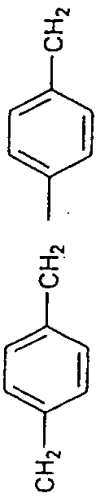
Compound No.	A	B
1	$(CH_2)_{10}$	
2	$(CH_2)_{10}$	
3	$(CH_2)_{10}$	
4	$(CH_2)_{10}$	
5	$(CH_2)_{10}$	

$(CH_2)_{10}$				
				
6	7	8	9	10

11		
12		
13		
14		
15		
16		

17		
18		
19		
20		
21	$(CH_2)_8$	$(CH_2)_8$
22	$(CH_2)_{10}$	$(CH_2)_{10}$
23	$(CH_2)_6$	$(CH_2)_6$
24	$(CH_2)_5$	$(CH_2)_5$
25	$(CH_2)_5$	$(CH_2)_4$
26	$(CH_2)_5$	$(CH_2)_6$
27	$(CH_2)_4$	$(CH_2)_4$

28	$(CH_2)_4$	$(CH_2)_5$
29	$(CH_2)_3$	$(CH_2)_5$
30	$(CH_2)_3$	$(CH_2)_4$
31	$(CH_2)_3$	$(CH_2)_3$
32	$(CH_2)_3$	$(CH_2)_3$
33		$(CH_2)_5$
34		$(CH_2)_4$
35		$(CH_2)_6$
36		$(CH_2)_3$

37	$(CH_2)_6$	
38	$(CH_2)_5$	
39	$(CH_2)_4$	
40	$(CH_2)_3$	
41	$(CH_2)_6$	$(CH_2)_5$
A	$(CH_2)_{10}$	

Intermediate I

1,10-Di(quinoline-4-yl)aminodecane:

4-chloroquinoline (2 g, 12.2 mmol) and 1,10-diaminodecane (1.054 g, 6.12 mmol) were dissolved with heating in 1-pentanol (40 ml) and heated under reflux for 30 h. On cooling a creamy precipitate formed which was collected, dissolved in MeOH, made alkaline with 10% aqueous NaOH, diluted with water and left overnight. The product was collected, and crystallised (MeOH) and had mp: 169-171°C. Analysis for $C_{28}H_{34}N_4$, 0.3 CH_3OH, 0.2 H_2O. Calculated:C, 77.28, H, 8.16; N, 12.74%. Found: C, 76.91; H, 7.77; N, 12.77%

Compound 1

7,18-Diaza-3,4(1,4)-dibenzena-1,6(1,4)-diquinolinacyclooctadecaphane tri-trifluoroacetate hydrate. Alternatively named: 1,1'-(*p,p'*-dimethylenebiphenyl)-N^4, $N^{4'}$, decamethylene-bis-(4-aminoquinolinium) tri-trifluoroacetate hydrate:

1,10-di(quinolin-4-yl)aminodecane (0.2 g, 0.469 mmol)(Intermediate I) and 4,4'-bis(bromomethyl)biphenyl (0.160 g, 0.470 mmol) were dissolved with heating in 2-butanone (50 ml) and then heated, with stirring, under reflux for 72 h. The product was collected by filtration and purified by preparative HPLC, then dissolved in the minimum amount

of cold 2-propanol, filtered by gravity and the solvent removed *in vacuo*. This yielded an off white solid, mp: 280-282 °C.

Analysis for $C_{42}H_{44}N_4$, 3.4 CF_3COOH, 1.4 H_2O.

Calculated:C, 57.59, H, 4.97; N, 5.5%. Found: C, 57.81; H, 5.31; N, 5.71%.

Compound 2

7,18-Diaza-3,4(1,3)-dibenzena-1,6(1,4)-diquinolinacyclooctadecaphane tetra-trifluoroacetate dihydrate. Alternatively named: 1,1'-(m,m'-dimethylenebiphenyl)- N^4, $N^{4'}$-decamethylene-bis-(4-aminoquinolinium) tetra-trifluoroacetate dihydrate: 1,10-di(quinolin-4-yl)aminodecane (0.120 g, 0.281 mmol)(Intermediate I) and 4,4'-bis(bromomethyl)biphenyl (0.096 g, 0.281 mmol) were dissolved with heating in 2-butanone (30 ml) and then heated, with stirring, under reflux for 39 h. The product was collected and purified as described above to yield an off-white solid, mp: 112-114 °C. Analysis for $C_{42}H_{44}N_4$, 4.2 CF_3COOH, 2.2 H_2O. Calculated: C, 53.89, H, 4.72; N, 4.99%. Found: C, 53.81; H, 4.94; N, 5.09%.

Compound 3

6,17-Diaza-3(2,7)-fluorena-1,5(1,4)-diquinolinacycloheptadecaphane tetra-trifluoroacetate

dihydrate. Alternatively named: 1,1'-(2,7-dimethylenefluorene)- N^4, $N^{4'}$-decamethylene-bis-(4-aminoquinolinium) tetra-trifluoroacetate dihydrate: 1,10-di(quinolin-4-yl)aminodecane (0.147 g, 0.344 mmol) (Intermediate I) and 2,7-di(bromomethyl)fluorene (0.120 g, 0.343 mmol) were dissolved with heating in 2-butanone (35 ml) and then heated, with stirring, under reflux for 39 h. The product was collected and purified as above to yield an off-white solid, mp: 214-216 °C. Analysis for $C_{43}H_{44}N_4$, 3.9 CF_3COOH, 2 H_2O. Calculated: C, 55.59, H, 4.77; N, 5.10%. Found: C, 55.57; H, 5.02; N, 5.03%.

Compound 4

9,20-Diaza-3,6(1,4)-dibenzena-1,8(1,4)-diquinolinacycloicosaphane tri-trifluoroacetate hydrate. Alternatively named: 1,1'-(*p,p'*-dimethylenebibenzyl)-N^4,$N^{4'}$-decamethylene-bis-(4-aminoquinolinium) tri-trifluoroacetate hydrate: 1,10-di(quinolin-4-yl)aminodecane (0.200 g, 0.469 mmol) (Intermediate I) and bis(*p*-bromomethyl)bibenzyl (0.173 g, 0.470 mmol) were dissolved with heating in 2-butanone (50 ml) and heated, with stirring, under reflux for 36 h. The product was purified as above to yield an off-white solid, mp: 202-204 °C. Analysis for $C_{43}H_{46}N_4$, 3.2 CF_3COOH, 1.2 H_2O. Calculated: C, 59.38,

H, 5.3; N, 5.5%. Found: C, 59.25; H, 5.38; N, 5.76%.

Compound 5

9,20-Diaza-3,6(1,4)-dibenzena-1,8(1,4)-diquinolina-4-(Z)-enecycloicosaphane tetra-trifluoroacetate dihydrate. Alternatively named: 1,1'-(*p,p'*-dimethylene-(Z)-stilbene)-N^4,$N^{4'}$-decamethylene-bis-(4-aminoquinolinium) tetra-trifluoroacetate dihydrate: 1,10-di(quinolin-4-yl)aminodecane (0.200 g, 0.469 mmol) (Intermediate I) and 4,4'-bis(bromomethyl)-(Z)-stilbene (0.172 g, 0.469 mmol) were dissolved with heating in 2-butanone (50 ml) and heated, with stirring, under reflux for 46 h. The product was collected and purified as described above to yield an off-white solid, mp: 184-186 °C. Analysis for $C_{44}H_{46}N_4$, 4.2 CF_3COOH, 2.2 H_2O. Calculated: C, 54.76, H, 4.79; N, 4.87%. Found: C, 54.85; H, 5.12; N, 4.88%.

Intermediate II

4,4'-Di-(quinolin-4-yl)aminomethylbiphenyl: 4-Chloroquinoline (1.6 g, 9.6 mmol) and 4,4'-di(aminomethyl)biphenyl (1.0 g, 4.8 mmol) were dissolved with heating in 1-pentanol (32 ml) and heated under reflux for 48 h. On cooling a creamy precipitate formed which was collected, dissolved in MeOH (350 ml), made alkaline with 10% aq NaOH diluted

with water and left overnight. The product formed was collected and crystallized from MeOH-$CHCl_3$-petroleum ether (bp 40-60 °C) and dried to give 1.5 g; mp: 250-252 °C dec.

Analysis for $C_{32}H_{26}N_4$, 0.8 CH_3OH. Calculated: C, 80.04, H, 5.98; N, 11.38%. Found: C, 80.12; H, 6.15; N, 11.28%.

Compound 6

13,18-Diaza-15,16(1,4)-dibenzena-1,12(1,4)-diquinolinacyclooctadecaphane tri-trifluoracetate hydrate. Alternatively named: 1,1'-decamethylene-N^4,$N^{4'}$-(*p*,*p'*-dimethylenebiphenyl)-bis-(4-aminoquinolinium) tri-trifluoroacetate hydrate: 4,4'-Di-(quinolin-4-yl)aminomethylbiphenyl (0.1 g, 0.214 mmol) (Intermediate II) and 1,10-diiododecane (0.09 g, 0.214 mmol) were dissolved with heating in 2-butanone (50 ml) and heated, with stirring, under reflux for 120 h. The product was collected by filtration (0.140 g) and then purified by preparative HPLC. The isolated product was dissolved in the minimum amount of cold 2-propanol, filtered by gravity and the solvent removed *in vacuo*. This yielded a yellow solid, mp: 233-234 °C dec.. Analysis for $C_{42}H_{44}N_4$, 3.1 CF_3COOH, 1.1 H_2O. Calculated: C, 59.19, H, 5.08; N, 5.73%. Found: C, 59.03; H, 5.14; N, 5.72%.

Compound 7

7,12-Diaza-3,4,9,10(1,4)-tetrabenzena-1,6(1,4)-diquinolinacyclododecaphane hexa-trifluoroacetate tetrahydrate. Alternatively named: 1,1'-(*p,p'*-Dimethylenebiphenyl)-N^4,$N^{4'}$-(*p,p'*-dimethylenebiphenyl)-bis-(4-aminoquinolinium) hexa-trifluoroacetate tetrahydrate:

4,4'-Di-(quinolin-4-yl)aminomethylbiphenyl (0.25 g, 0.536 mmol)(Intermediate II) and 4,4'-di(bromomethyl)biphenyl (0.18 g, 0.53 mmol) were dissolved with heating in 2-butanone (50 ml) and heated, with stirring, under reflux for 60 h. The product was collected by filtration (0.40 g) and then purified by preparative HPLC. The isolated product was dissolved in the minimum amount of cold 2-propanol, filtered by gravity and the solvent removed *in vacuo* to yield a solid, mp: 140-142 °C. Analysis for $C_{46}H_{36}N_4$, 6 CF_3COOH, 4 H_2O. Calculated: C, 49.72, H, 3.60; N, 4.00%. Found: C, 49.47; H, 3.91; N, 3.95%.

Intermediate III

***m*-Bis[(quinolin-4-yl)aminomethyl]benzene hydrate:**

4-Chloroquinoline (0.800 g, 0.489 mmol) and *m*-di(aminomethyl)benzene (0.340 g, 2.49 mmol) were dissolved with heating in 1-pentanol (20 ml) and heated

under reflux for 41.5 h and then evaporated to afford an oil which crystallized after 2 days. The latter was suspended in MeOH (120 ml), made alkaline with 10% aqueous NaOH (40 ml) and stirred for 3 h. The product was collected by filtration, dried, and crystallized from MeOH (120 ml) to give beige crystals, mp: 243-246 °C (decomp). Analysis for $C_{26}H_{22}N_4$, 1.7 H_2O. Calculated: C, 74.16, H, 6.08; N, 13.3%. Found: C, 74.06; H, 5.79; N, 12.97%.

Compound 8

6,10-Diaza-3,8(1,3)-dibenzena-1,5(1,4)-diquinolinacyclodecaphane di-trifluoroacetate dihydrate. Alternatively named: 1,1', N^4,$N^{4'}$-bis(m-dimethylenebenzene)-bis(4-aminoquinolinium) di-trifluoroacetate dihydrate:

m-Bis[(quinolin-4-yl)aminomethyl]-benzene (0.210 g, 0.0616 mmol)(Intermediate III) and *m*-di(bromomethyl)-dibenzene (0.146 g, 0.0553 mmol) were dissolved with heating in 2-butanone (25 ml) and heated, with stirring, under reflux for 23 h. The product was collected by filtration (0.333 g) and purified by preparative HPLC. The resulting product was then dissolved in the minimum amount of cold 2-propanol, filtered by gravity and the solvent removed *in vacuo* to yield a white microcrystalline compound; mp: 224-226 °C

(decomp). Analysis for $C_{34}H_{28}N_4$, 2 CF_3COOH, 2.4 H_2O. Calculated: C, 59.75, H, 4.59; N, 7.33%. Found:C, 59.77; H, 4.70; N, 7.12.%.

Compound 9

6,10-Diaza-8,(1,3),3(1,4)-dibenzena-1,5(1,4)-diquinolinacyclodecaphane di-trifluoroacetate hydrate. Alternatively named: [1,1'-(*p*-dimethylenebenzene)-N^4,$N^{4'}$-(*m*-dimethylenebenzene)]-bis(4-aminoquinolinium) di-trifluoroacetate hydrate:

Likewise *m*-bis[(quinolin-4-yl)aminomethyl]-benzene (0.210 g, 0.0538 mmol)(Intermediate III) and *p*-di(bromomethyl)-benzene (0.146 g, 0.0553 mmol) were heated together in 2-butanone (30 ml) for 23 h and the product purified by preparative HPLC to yield a white powder, mp: 234-236 °C (decomp). Analysis for $C_{34}H_{28}N_4$, 2 CF_3COOH, 1.1 H_2O. Calculated: C, 56.22, H, 3.92; N, 6.56%. Found: C, 55.94, H, 4.00; N, 6.38%.

Intermediate IV

***p*-Bis[(quinolin-4-yl)aminomethyl]benzene (a starting product):**

4-Chloroquinoline (0.80 g, 4.89 mmol) and *p*-bis(aminomethyl)benzene (0.34 g, 2.49 mmol) were heated in 1-pentanol (20 ml) under reflux for 41.5 h. In the course of the reaction a creamy precipitate formed

which was collected by vacuum filtration. The 1-pentanol filtrate was concentrated to dryness and the resulting oil left to solidify (2 days). The two products were combined and suspended in MeOH (120 ml), made alkaline with aqueous NaOH (10%, 40 ml) and stirred for 3 h. The product was filtered off, dried, and recrystallized (MeOH, 120 ml) to give cream crystals (0.573 g, 57.7 %); mp: 278-279°C (decomp). Analysis for $C_{26}H_{22}N_4$, 0.4 H_2O. Calculated: C, 78.52, H, 5.78; N, 14.09%. Found: C, 78.46; H, 5.90; N, 13.92%.

Compound 10

6,10-Diaza-3(1,3),8(1,4)-dibenzena-1,5(1,4)-diquinolinacyclodecaphane tri-trifluoroacetate hydrate.

Alternatively named: [1,1'-(*m*-dimethylene- benzene)-N^4,$N^{4'}$-(*p*-dimethylenebenzene)]-bis(4-aminoquinolinium) tri-trifluoroacetate hydrate:

p-Bis[(quinolin-4-yl)aminomethyl]benzene (0.180 g, 0.046 mmol)(Intermediate IV) and *m*-di(bromo-methyl)benzene (0.122 g, 0.046 mmol) were dissolved with heating in 2-butanone (25 ml) and heated with stirring under reflux for 23 h. The resulting product was filtered off and purified by preparative HPLC; it was then dissolved in the minimum amount of cold 2-propanol, filtered, and the solvent was removed *in*

vacuo to yield the white crystalline product; mp: 255-257 °C (decomp). Analysis for $C_{34}H_{28}N_4$, 3 CF_3COOH, H_2O. Calculated: C, 56.34, H, 3.90; N, 6.57%. Found:C, 56.72, H, 4.21; N, 6.42%.

Compound 11

3^2-Hydroxy-6,10-diaza-3(1,3),8(1,4)-dibenzena-1,5(1,4)-diquinolinacyclodecaphane trihydrobromide methanolate.

Alternatively named: **[1,1'-(1,3-dimethylene-2-hydroxybenzene)-N^4,$N^{4'}$-(1,4-dimethylenebenzene)]-bis-(4-aminoquinolinium) dibromide hydrobromide methanolate:**

A mixture of 2,6-dimethylanisole (1.8 g, 14 mmol), N-bromosuccinimide (4.9 g, 30 mmol) and dibenzoyl peroxide (0.4 g, 1.8 mmol) in carbon tetrachloride (50 ml) was stirred and heated under reflux for 4 h, cooled and filtered to remove the solid. The solvent was distilled off to give an oil which solidified on cooling and was crystallised from hexane ethylacetate to give 2,6-di(bromomethyl)anisole as a pale yellow crystalline solid, mp: 90-91 °C.

To the latter (1.28 g, 4.25 mmol) in dichloromethane (50 ml) was added boron tribromide (0.53 g, 2.15 mmol) as a 1M solution in dichloromethane. The mixture was heated under reflux with stirring for 18 h, cooled and poured onto icewater (100 ml). The organic layer was

separated, dried ($MgSO_4$) and evaporated to yield 2,6-di(bromomethyl)phenol, mp: 80-82 °C.

To a refluxing solution of *p*-bis[(quinolin-4-yl)aminomethyl]-benzene (0.2 g, 0.051 mmol)(Intermediate IV) in 2-butanone (40 ml) was added 2,6-di(bromomethyl)phenol (0.17 g, 0.060 mmol) dissolved in 2-butanone (5 ml) and the mixture was heated with stirring under reflux for 42 h. The product was collected by filtration and crystallised from methanol to yield a pale yellow crystalline solid, mp: 280-282 °C decomp. Analysis for $C_{34}H_{28}N_4O$, 3 HBr, CH_3OH. Calculated: C, 53.66, H, 4.50; N, 7.15%. Found: C, 53.56, H, 4.54; N, 6.86%.

Compound 12

3^2-Hydroxy-3^5-iodo-6,10-diaza-3(1,3),8(1,4)-dibenzena-1,5(1,4)-diquinolinacyclodecaphane dihydroiodide methanolate hemihydrate. Alternatively named: [1,1'-(1,3-dimethylene-2-hydroxy-5-iodobenzene)-N^4,$N^{4'}$-(1,4-dimethylenebenzene)]-bis-(4-aminoquinolinium) diiodide methanolate hemihydrate.

To a solution of the above cyclophane Compound 11 (0.01 g, 0.162 mmol) and sodium iodide (0.0029 g, 0.195 mmol) in DMF (0.8 ml) at 28 °C was added chloramine T (0.0055 g, 0.195 mmol) and the mixture was stirred at 28 °C for

1 h, then diluted with water (2 ml) and acidified with 5% HCl. The solid which separated was filtered off, washed with water (2 ml), then with sodium thiosulphite solution, and dried to afford a solid which, after crystallisation from methanol, yielded the product as a yellow solid, mp: 260 °C decomp. Analysis for $C_{34}H_{27}IN_4O$, 2 HI, CH_3OH, 0.5 H_2O. Calculated: C, 45.14, H, 3.68; N, 6.01%. Found: C, 45.37, H, 3.62; N, 5.60%.

Compound 13

3^2-Methoxy-6,10-diaza-3(1,3),8(1,4)-dibenzena-1,5(1,4)-diquinolinacyclodecaphane dihydrobromide dihydrate.

Alternatively named: [1,1'-(1,3-dimethylene-2-methoxybenzene)-N^4,$N^{4'}$-(1,4-dimethylenebenzene)]-bis-(4-aminoquinolinium) dibromide dihydrate.

To a refluxing solution of *p*-bis[(quinolin-4-yl)aminomethyl]-benzene (0.15 g, 0.038 mmol)(**Intermediate IV**) in 2-butanone (30 ml) was added 2,6-di(bromomethyl)anisole (0.14 g, 0.05 mmol) dissolved in 2-butanone (5 ml) and the mixture was heated with stirring under reflux for 42 h. The product was collected by filtration and crystallised from methanol to give an off white solid, mp: 282-285 °C decomp. Analysis for $C_{35}H_{30}N_4O$, 2 HBr, 2 H_2O. Calculated: C, 58.35, H, 5.04; N, 7.78%. Found: C,

58.60, H, 4.94; N, 7.55%.

Compound 14

6,10-Diaza-3,8(1,4)-dibenzena-1,7(1,4)-diquinolinacyclodecaphane tri-trifluoroacetate hydrate.

Alternatively named: [1,1',N^4,N^4'-bis(*p*-dimethylenebenzene)]-bis(4-aminoquinolinium) tri-trifluoroacetate hydrate:

p-Bis [(quinolin-4-yl)aminomethyl]benzene (0.180 g, 0.046 mmol) (Intermediate IV) and *p*-di(bromomethyl)benzene (0.122 g, 0.046 mmol) were dissolved with heating in 2-butanone (25 ml) and heated with stirring under reflux for 23 h. The resulting product was filtered off and purified by preparative HPLC; it was then dissolved in the minimum amount of cold 2-propanol, filtered, and the solvent was removed *in vacuo* to yield the white solid product; mp: 326-328 °C (decomp). Analysis for $C_{34}H_{28}N_4$, 3 CF_3COOH, 1.2 H_2O. Calculated: C, 56.11, H, 3.93; N, 6.54%. Found:C, 56.10, H, 4.19; N, 6.38%.

Intermediate V

4,4'-Bis[(quinolin-4-yl)aminomethyl]diphenylmethane dimethanolate:

4-Chloroquinoline (1.45 g, 9 mmol) and 4,4'-bis(aminomethyl)diphenylmethane (1 g, 4.42 mmol) were

dissolved with heating in 1-pentanol (50 ml) and then heated under reflux for 47 h. The suspension was then concentrated to dryness and the resulting solid (3.26 g) was dissolved in MeOH (100 ml), made alkaline with aqueous NaOH (10 %, 40 ml), and stirred for 19 h. The product was filtered off and dried, and purified by column chromatography (MeOH:$CHCl_3$=1:1) to give a yellowish powder; this was dissolved in dry 2-propanol, filtered, and dried; mp: 116-118 °C (decomp). Analysis for $C_{33}H_{28}N_4$, 2.3 CH_3OH, 0.1 H_2O. Calculated: C, 76.24, H, 6.78; N, 10.07%. Found: C, 76.51, H, 6.72; N, 9.72.%.

Compound 15

8,14-Diaza-3,5,10,12(1,4)-tetrabenzena-1,7(1,4)-diquinolinacyclotetradecaphane tri-trifluoroacetate dihydrate. Alternatively named: 1,1',N^4,$N^{4'}$-[*p*,*p*'-dimethylenediphenylmethane-bis(4-amino-quinolinium)] tri-trifluoroacetate dihydrate:

4,4'-Bis [(quinolin-4-yl)aminomethyl]-diphenylmethane (0.271 g, 0.0564 mmol)(Intermediate V) and 4,4'-bis(bromomethyl)diphenylmethane (0.200 g, 0.0565 mmol) were dissolved with heating in 2-propanone (50 ml) and heated with stirring under reflux for 45 h. The product was collected by filtration and purified by preparative HPLC; it was then dissolved in the minimum

amount of cold 2-propanol, filtered, and the solvent removed *in vacuo*. This yielded an off-white microcrystalline compound; mp: 218-220 °C (decomp). Analysis for $C_{48}H_{40}N_4$, 3 CF_3COOH, 2.2 H_2O. Calculated: C, 61.50, H, 4.53; N, 5.31%. Found: C, 61.32, H, 4.59; N, 5.24%.

In a similar manner, the following compounds were synthesised:

Compound 16

7,13-Diaza-3,4,9,11(1,4)-tetrabenzena-1,6(1,4)-diquinolinacyclotridecaphane tetra-trifluoroacetate dihydrate. Alternatively named: [1,1'-(*p,p'*-dimethylenebiphenyl)-N^4,$N^{4'}$-(*p,p'*-dimethylene-diphenylmethane)]-bis(4-aminoquinolinium) tetra-trifluoroacetate dihydrate:

From 4,4'-bis[(quinolin-4-yl)aminomethyl]-diphenylmethane (0.283 g, 0.0588 mmol)(Intermediate V) and 4,4'-bis(bromo-methyl)biphenyl (0.200 g, 0.0588 mmol) to yield a white microcrystalline compound; mp: 224-226 °C (decomp). Analysis for $C_{48}H_{40}N_4$, 4 CF_3COOH, 2 H_2O. Calculated: C, 57.4, H, 4.03; N, 4.87%. Found: C, 57.72, H, 4.36; N, 4.69%.

Compound 17

9,15-Diaza-3,6,11,13(1,4)-tetrabenzena-1,8(1,4)-diquinolina-4-(Z)-ene-cyclopentadecaphane di-trifluoroacetate trihydrate. Alternatively named: [1,1'-(*p,p'*-dimethylene-(Z)-stilbene)-N^4,$N^{4'}$-(*p,p'*-dimethylenediphenylmethane)]-bis(4-aminoquinolinium) di-trifluoroacetate trihydrate:

From 4,4'-bis[(quinolin-4-yl)aminomethyl]diphenylmethane (0.263 g, 0.0547 mmol) (Intermediate V) and 4,4'-bis(bromomethyl)-(Z)-stilbene (0.200 g, 0.0546 mmol) to give the product which was recrystallised from absolute ethanol after the addition of a few drops of diethyl ether to yield a white powder; mp: 267-269 °C (decomp). Analysis for $C_{48}H_{40}N_4$, 2 CF_3COOH, 3.4 H_2O. Calculated: C, 65.21, H, 5.25; N, 5.74%. Found: C, 65.43, H, 5.17; N, 5.75%.

Compound 18

8,14-Diaza-3,5,10,12(1,4)-tetrabenzena-4(2,6)-pyridina-1,7(1,4)-diquinolinacyclotetradecaphane tri-trifluoroacetate trihydrate dimethanolate. Alternatively named: 1,1'-{[2,6-bis(4'-methylenephenyl)pyridine]-N^4,$N^{4'}$-(*p,p'*-dimethylenediphenylmethane)}-bis(4-aminoquinolinium) tri-trifluoroacetate trihydrate dimethanolate:

4,4'-bis[(quinolin-4-yl)aminomethyl]diphenylmethane (0.200 g, 0.0416 mmol) (Intermediate V) and 2,6-bis[4'-

(bromomethyl) phenyl]pyridine were dissolved with heating in 2-propanone (30 ml). The solution was heated with stirring under reflux for 40 h and the product collected by filtration. This was treated with boiling EtOH (75 ml) and the insoluble material was filtered off and purified by preparative HPLC. The isolated product was then dissolved in the minimum amount of cold 2-propanol, filtered by gravity and the solvent removed *in vacuo* to yield an off-white solid; mp: 224-226 °C. Analysis for $C_{52}H_{40}N_5$, 3 CF_3COOH, 2 CH_3OH, 2.8 H_2O. Calculated: C, 60.48, H, 4.79; N, 5.88%.Found: C, 60.49, H, 4.89; N, 5.53%.

Intermediate VI

4,4'-Bis[(quinolin-4-yl)aminomethyl]biphenyl hydrate (a starting product):

In a similar manner to Intermediate V 4-chloroquinoline (0.231 g, 1.41 mmol) and 4,4'-bis(aminomethyl)biphenyl (0.150 g, 0.707 mmol) were heated together in 1-pentanol, and the suspension stirred under reflux for 47 h. The product, after being recrystallized [MeOH, $CHCl_3$, petroleum ether (bp: 60-80 °C)] was obtained as cream crystals; mp: 250-252 °C (decomp). Analysis for $C_{26}H_{22}N_4$, 1.6 H_2O. Calculated: C, 77.58, H, 5.94; N, 11.31%. Found:C, 77.54, H, 5.67; N, 11.02%

Compound 19

7,13-Diaza-3,4,9,11(1,4)-tetrabenzena-1,6(1,4)-diquinolinacyclotridecaphane tetra-trifluoroacetate heptahydrate. Alternatively named: [1,1'-(*p,p'*-dimethylenebiphenyl)-N^4,$N^{4'}$-(*p,p'*-dimethylenediphenylmethane)]-bis(4-aminoquinolinium) tetra-trifluoroacetate heptahydrate:

From 4,4'-bis[(quinolin-4-yl)aminomethyl]biphenyl (0.173 g, 0.0371 mmol)(Intermediate VI) and 4,4'-bis(bromomethyl)diphenylmethane (0.131 g, 0.0370 mmol). The isolated product was obtained as an off-white solid; mp: > 350 °C. Analysis for $C_{48}H_{40}N_4$, 4.5 CF_3COOH, 7 H_2O. Calculated: C, 51.82, H, 4.39; N, 4.32%. Found: C, 52.05, H, 4.62; N, 4.16.%.

Compound 20

6,11-Diaza-8,9(1,4)-dibenzena-3(2,7)-fluorena-1,5(1,4)-diquinolinacycloundecaphane tetra-trifluoroacetate hexahydrate. Alternatively named: [1,1'-(2,7-dimethylenefluorene)-N^4,$N^{4'}$-(*p,p'*-dimethylenebiphenyl)]-bis(4-aminoquinolinium) tetra-trifluoroacetate hexahydrate:

From 4,4'-bis[(quinolin-4-yl)aminomethyl]biphenyl (0.200 g, 0.0429 mmol)(Intermediate VI) and 2,7-bis(bromomethyl)fluorene (0.154 g, 0.0429 mmol) with heating in 2-propanone (50 ml) under reflux for 39 h.

After filtration, the collected product was treated with a boiling mixture of EtOH/MeOH (150 ml/50 ml) and the insoluble sample was filtered and purified by preparative HPLC to yield an off-white solid; mp: 316-319 °C. Analysis for $C_{47}H_{36}N_4$, 4 CF_3COOH, 6.6 H_2O. Calculated: C, 53.63, H, 4.35; N, 4.55%. Found: C, 53.63, H, 4.58; N, 4.41%.

Compound 21

11,20-Diaza-1,10(1,4)-diquinolinacycloicosaphane dihydroiodide sesquihydrate. Alternatively named: **1,1'-(Octane-1,8-diyl)-N^4,$N^{4'}$-(octane-1,8-diyl)-bis-(4-aminoquinolinium) diiodide sesquihydrate.**

A mixture of 4-chloroquinoline (0.5 g, 3.056 mmol) and 1,8-diaminooctane (0.220 g, 1.528 mmol) in 1-pentanol (10 ml) was heated under reflux with stirring for 48 h and then cooled. The resulting precipitate was collected, washed with 1-pentanol and diethyl ether, then dissolved in 12 ml of hot methanol, and basified with 3.5 ml of 1M NaOH solution. Water (30 ml) was added into the flask and it was cooled for 1 h. The precipitate was collected, washed extensively with water, and then dried under vacuum at 40 °C for 12 h to give N^4, $N^{4'}$-(octane-1,8-diyl)-bis-(4-aminoquinoline) as a white crystalline solid (0.6 g, 98% yield); mp: 185-189 °C.

A mixture of N^4, $N^{4'}$-(octane-1,8-diyl)-bis-(4-aminoquinoline) (0.4 g, 1.004 mmol) and 1,8-diiodooctane (0.367 g, 1.004 mmol) in 2-butanone (330 ml) was heated under reflux with stirring for 7 days and then cooled. The resulting precipitate was collected, washed extensively with diethyl ether, dried under vacuum at 40 °C for 12 h to give the product as a yellowish crystalline solid; mp: 248-253 °C. Analysis for $C_{34}H_{46}N_4I_2$, 1.5 H_2O. Calculated: C, 51.57, H, 6.24; N, 7.08%. Found: C, 51.68, H, 5.99; N, 6.78%.

Compound 22

13,24-Diaza-1,12(1,4)-diquinolinacyclotetraicosaphane tri-trifluoroacetate. Alternatively named: 1,1'-(Decane-1,10-diyl)-N^4, $N^{4'}$-(decane-1,10-diyl)-bis-(4-aminoquinolinium) tri-trifluoroacetate.

A mixture of N^4, $N^{4'}$-(decane-1,10-diyl)-bis-(4-aminoquinoline) prepared in the same way as the intermediate in the synthesis of Compound 21 (0.4 g, 0.9 mmol) and 1,10-diiododecane (0.37 g, 0.9 mmol) in 2-propanone (330 ml) was heated under reflux with stirring for 7 days, then cooled. The resulting precipitate was collected, washed extensively with diethyl ether, and purified by preparative HPLC to give a white crystalline solid; mp: 122-125 °C. Analysis for $C_{38}H_{52}N_4$, 3 CF_3COOH. Calculated: C, 58.25, H, 6.12; N, 6.18%. Found: C, 58.53, H, 6.12; N, 6.14%.

Compound 23

9,16-Diaza-1,8(1,4)-diquinolinacyclohexadecaphane tetra-trifluoroacetate. Alternatively named: 1,1'-(Hexane-1,6-diyl)-N^4, $N^{4'}$-(hexane-1,6-diyl)-bis-(4-aminoquinolinium) tetra- trifluoroacetate.

A mixture of 4-chloroquinoline (0.5 g, 3.05 mmol) and hexamethylenediamine (0.177 g, 1.52 mmol) in 1-pentanol (10 ml) was heated under reflux with stirring for 48 hours and then cooled. The resulting precipitate was collected, washed with 1-pentanol and diethyl ether and then treated as described above in the synthesis of Compound 21 to give N^4, $N^{4'}$-(hexane-1,6-diyl)-bis-(4-aminoquinoline) as a white crystalline solid (0.55 g, 97% yield); mp: 226-230 °C.

A mixture of N^4, $N^{4'}$-(hexane-1,6-diyl)-bis-(4-aminoquinoline) (0.4 g, 1.080 mmol) and 1,6-diiodohexane (0.365 g, 1.080 mmol) in 2-butanone (330 ml) was heated under reflux with stirring for 7 days and then cooled. The precipitate was collected by filtration, washed extensively with diethyl ether, and purified by preparative HPLC, to give the product as a white crystalline solid; mp: 132-136 °C. Analysis for $C_{30}H_{36}N_4$, 4 CF_3COOH. Calculated: C, 50.21, H, 4.44; N, 6.17%. Found: C, 50.10, H, 4.43; N, 6.03%.

Compound 24

8,14-Diaza-1,7(1,4)-diquinolinacyclotetradecaphane tetra-trifluoroacetate. Alternatively named: 1,1'-(Pentane-1,5-diyl)-N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinolinium) tetra-trifluoroacetate.

A mixture of 4-chloroquinoline (0.5 g, 3.056 mmol) and 1,5-diaminopentane (0.156 g, 1.528 mmol) in 1-pentanol (10 ml) was heated under reflux with stirring for 48 hours and then cooled. Ether (20 ml) was added and the resulting precipitate was collected, washed with 1-pentanol and diethyl ether and then treated as described above in the synthesis of Compound 21 to give N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinoline) as a white crystalline solid, mp: 204-208 °C. A mixture of N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinoline) (0.475 g, 1.334 mmol) and 1,5-diiodopentane (0.432 g, 1.33 mmol) in 2-butanone (150 ml) was heated under reflux with stirring for 7 days and then cooled. The resulting precipitate was collected, washed extensively with diethyl ether and purified by preparative HPLC to give the product as a white crystalline solid; mp: 126-130 °C. Analysis for $C_{28}H_{32}N_4$, 4.2 CF_3COOH. Calculated: C, 48.37, H, 4.04; N, 6.20%. Found: C, 48.46, H, 3.99; N, 6.27%.

Compound 25

7,13-Diaza-1,6(1,4)-diquinolinacyclotridecaphane di-trifluoroacetate. Alternatively named: 1,1'-(Butane-1,4-diyl)-N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinolinium) di-trifluoroacetate:

This was prepared similarly to Compound 24 from N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinoline) (0.50 g, 1.41 mmol) and 1,4-diiodobutane (0.45 g, 1.45 mmol) in 2-butanone (170 ml) heated under reflux for 6 days. The mixture was cooled and the resulting solid was collected, washed well with ether and purified by preparative HPLC to give the product as a white crystalline solid, mp: 201-203 °C. Analysis for $C_{27}H_{30}N_4$, 2.3 CF_3COOH. Calculated: C, 56.41, H, 4.84; N, 8.33%. Found: C, 56.44, H, 4.82; N, 8.36%.

Compound 26

9,15-Diaza-1,8(1,4)-diquinolinacyclopentadecaphane tri-trifluoroacetate. Alternatively named: 1,1'-(Hexane-1,6-diyl)-N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinolinium) tri-trifluoroacetate:

This was prepared similarly to Example 24 from N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinoline) (0.355 g, 1.00 mmol) and 1,6-diiodohexane (0.30 g, 0.99 mmol) in 2-butanone (125 ml) heated under reflux for 6 days. The mixture was cooled and the resulting solid was

collected, washed well with ether and purified by preparative HPLC to give the product as a white crystalline solid, mp: 195-198 °C. Analysis for $C_{29}H_{36}N_4$, 3.1 CF_3COOH. Calculated: C, 53.38, H, 4.72; N, 7.07%. Found: C, 53.24, H, 4.64; N, 7.17%.

Compound 27

7,12-Diaza-1,6(1,4)-diquinolinacyclododecaphane tetra-trifluoroacetate. Alternatively named: 1,1'-(Butane-1,4-diyl)-N^4, $N^{4'}$-(butane-1,4-diyl)-bis-(4-aminoquinolinium) tetra-trifluoroacetate:

A mixture of 4-chloroquinoline (0.5 g, 3.05 mmol) and 1,4-diaminobutane (0.134 g, 1.52 mmol) in 1-pentanol (10 ml) was heated under reflux with stirring for 48 h and then cooled. Ether (20 ml) was added to the mixture and the resulting precipitate was collected, washed with 1-pentanol and diethyl ether and treated as described above in the synthesis of Compound 21 to give N^4, $N^{4'}$-(butane-1,4-diyl)-bis-(4-aminoquinoline) as a white crystalline solid; mp: 258-264 °C.

A mixture of N^4, $N^{4'}$-(butane-1,4-diyl)-bis-(4-aminoquinoline) (0.22 g, 0.643 mmol) and 1,4-diiodobutane (0.199 g, 0.643 mmol) in 2-butanone (150 ml) was heated under reflux with stirring for 7 days and then cooled. The resulting precipitate was

collected, washed extensively with diethyl ether and purified by preparative HPLC to give the product as a white crystalline solid; mp: 138-140 °C. Analysis for $C_{26}H_{28}N_4$, 4.1 CF_3COOH. Calculated: C, 47.52, H, 3.75; N, 6.47%. Found: C, 47.40, H, 3.74; N, 6.43%.

Compound 28

8,13-Diaza-1,7(1,4)-diquinolinacyclotridecaphane tri-trifluoroacetate. Alternatively named: 1,1'-(Pentane-1,5-diyl)-N^4, $N^{4'}$-(butane-1,4-diyl)-bis-(4-aminoquinolinium) tri-trifluoroacetate:

This was prepared similarly to Compound 27 from N^4, $N^{4'}$-(butane-1,4-diyl)-bis-(4-aminoquinoline) (0.26 g, 0.75 mmol) and 1,5-diiodopentane (0.21 g, 0.75 mmol) in 2-butanone (85 ml) heated under reflux for 6 days. The mixture was cooled and the resulting solid was collected, washed well with ether and purified by preparative HPLC to give the product as a white crystalline solid, mp: 224-226 °C. Analysis for $C_{27}H_{30}N_4$, 2.7 CF_3COOH. Calculated: C, 54.17, H, 4.59; N, 7.80%. Found: C, 54.32, H, 4.53; N, 7.85%.

Compound 29

8,12-Diaza-1,7(1,4)-diquinolinacyclododecaphane tri-trifluoroacetate. Alternatively named: 1,1-(Pentane-1,5-diyl)-N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-

aminoquinolinium) tri-trifluoroacetate:

A mixture of 4-chloroquinoline and 1,3-diaminopropane (0.113 g, 1.53 mmol) in 1-pentanol (10 ml) was heated under reflux with stirring for 48 h and then cooled. Ether (20 ml) was added into the mixture and the resultant precipitate was collected, washed with 1-pentanol and diethyl ether and treated as described above in the synthesis of Compound 21 to give N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-aminoquinoline), as a white crystalline solid; mp: 302-306 °C.

A mixture of N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-aminoquinoline) (0.2 g, 0.609 mmol) and 1,5-diiodopentane (0.197 g, 0.609 mmol) in 2-butanone (68 ml) was heated under reflux with stirring for 7 days and then cooled. The resulting precipitate was washed extensively with diethyl ether and purified by preparative HPLC to give the product as a white crystalline solid; mp: 140-144 °C. Analysis for $C_{26}H_{28}N_4$, 3.2 CF_3COOH. Calculated: C, 51.09, H, 4.13; N, 7.36%. Found: C, 51.34, H, 4.10; N, 7.31%.

Compound 30

7,11-Diaza-1,6(1,4)-diquinolinacycloundecaphane tri-trifluoroacetate. Alternatively named: 1,1'-(Butane-1,4-diyl)-N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-

aminoquinoquinolinium) tri-trifluoroacetate:
From N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-aminoquinoline) (0.3 g, 0.914 mmol) and 1,4-diiodobutane (0.283 g, 0.914 mmol) in 2-butanone (250 ml) heated under reflux with stirring for 11 days. It was obtained as a yellowish crystalline solid; mp: 132-134 °C. Analysis for $C_{25}H_{26}N_4$, 3.4 CF_3COOH. Calculated: C, 49.57, H, 3.85; N, 7.28%. Found: C, 49.61, H, 3.78; N, 7.36%.

Compound 31

6,10-Diaza-1,5(1,4)-diquinolinacyclodecaphane tri-trifluoroacetate. Alternatively named: 1,1'-(Propane-1,3-diyl)-N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-aminoquinolinium) tri-trifluoroacetate:
This was prepared in a similar manner to Compound 29 from N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-aminoquinoline) (0.2 g, 0.609 mmol) and 1,3-diiodopropane (0.180 g, 0.609 mmol) in 4-methyl-2-pentanol (58 ml) heated under reflux with stirring for 6 days. It was obtained as a green-yellowish crystalline solid and contained about 7% of Compound 32; mp: 138-140 °C. Analysis for $C_{24}H_{24}N_4$, 3.2 CF_3COOH. Calculated: C, 49.62, H, 3.86; N, 7.63%. Found: C, 49.79, H, 3.74; N, 7.64%.

Compound 32

The above reaction procedure was repeated and the

initially formed solid product was collected and 0.4 g heated in trifluoroacetic acid (2.5 ml) and MeOH (7.5 ml) under reflux with stirring for 7 days. Preparative HPLC was then used to separate an isomer of the above Compound 31 (cis or trans isomer). It contained about 12% of Compound 31; mp: 215-217 °C. Analysis for $C_{24}H_{24}N_4$, 3.2 CF_3COOH, 0.5 H_2O. Calculated: C, 49.19, H, 3.83; N, 7.55%. Found: C, 49.47, H, 4.20; N, 7.45%.

Compound 33

8,12-Diaza-10(1,4)-benzena-1,7(1,4)-diquinolinacyclododecaphane di-trifluoroacetate.

Alternatively named: 1,1'-(Pentane-1,5-diyl)-N^4, $N^{4'}$-(*p*-dimethylenebenzene)-bis-(4-aminoquinolinium) di-trifluoroacetate:

4-Chloroquinoline (3.0 g, 18.3 mmol) and *p*-di(aminomethyl)benzene (1.25 g, 9.17 mmol) in 1-pentanol (60 ml) were heated under reflux with stirring for 2 days, then cooled. The resulting precipitate was collected, suspended in 300 ml of methanol, basified with 150 ml of 10% NaOH solution and stirred overnight. The solid was filtered off, washed extensively with water, dried at 40 °C under vacuum for 4 h to give N^4, $N^{4'}$-(*p*-dimethylenebenzene)-bis(4-aminoquinoline) as a pale yellow solid; mp: 278-280 °C(dec).

A mixture of N^4, $N^{4'}$-(*p*-dimethylenebenzene)-bis-(4-aminoquinoline) (0.5 g, 1.28 mmol) and 1,5-diiodopentane (0.41 g, 1.28 mmol) in 2-butanone (83 ml) was heated under reflux with stirring for 2 days, then cooled. The resulting precipitate was collected, washed extensively with diethyl ether and purified by preparative HPLC to give the product as a white crystalline solid, which was dried in vacuo at 40 °C for 3 days and had mp: 308-310 °C. Analysis for $C_{31}H_{30}N_4$, 2.2 CF_3COOH. Calculated: C, 59.93, H, 4.57; N, 7.90%. Found: C, 59.70, H, 4.60; N, 7.80%.

Compound 34

7,11-Diaza-9(1,4)-benzena-1,6(1,4)-diquinolinacycloundecaphane di-trifluoroacetate sesquihydrate. Alternatively named: 1,1'-(Butane-1,4-diyl)-N^4, $N^{4'}$(*p*-dimethylenebenzene)-bis-(4-aminoquinoline) ditrifluoroacetate sesquihydrate:

This was prepared in a similar manner to Compound 33 from N^4, $N^{4'}$-(*p*-dimethylenebenzene)-bis-(4-aminoquinolinium) and 1,4-diiodobutane and obtained as a white crystalline solid; mp: 248-250 °C(dec). Analysis for $C_{30}H_{28}N_4$, 2 CF_3COOH, 1.5 H_2O. Calculated: C, 58.35, H, 4.76; N, 8.01%. Found: C, 58.19, H, 4.91; N, 8.23%.

Compound 35

9,13-Diaza-11(1,4)-benzena-1,8(1,4)-diquinolinacyclotridecaphane di-trifluoroacetate.

Alternatively named: 1,1'-(Hexane-1,6-diyl)-N^4, $N^{4'}$-(*p*-dimethylenebenzene)-bis-(4-aminoquinolinium) di-trifluoroacetate:

This was similarly prepared from N^4, $N^{4'}$-(*p*-dimethylenebenzene)-bis-(4-aminoquinolinium) and 1,6-diiodohexane and obtained as a white crystalline solid; mp: 251-253 °C. Analysis for $C_{32}H_{32}N_4$, 2.2 CF_3COOH. Calculated: C, 60.43, H, 4.76; N, 7.74%. Found: C, 60.73, H, 5.00; N, 7.94%.

Compound 36

6,10-Diaza-8(1,4)-benzena-1,5(1,4)-diquinolinacyclodecaphane tri-trifluoroacetate.

Alternatively named: 1,1'-(Propane-1,3-diyl)-N^4, $N^{4'}$-(*p*-dimethylenebenzene)-bis-(4-aminoquinoline) tri-trifluoroacetate:

This was prepared similarly to Compound 33 from N^4, $N^{4'}$-(*p*-dimethylenebenzene)-bis-(4-aminoquinolinium) and 1,3-diiodopropane and obtained as a white crystalline solid; mp: 240-242 °C. Analysis for $C_{29}H_{26}N_4$, 3.1 CF_3COOH. Calculated: C, 53.93, H, 3.74; N, 7.15%. Found: C, 54.03, H, 3.87; N, 7.34%.

Compound 37

6,13-Diaza-3(1,3)-benzena-1,5(1,4)-diquinolinacyclotridecaphane di-trifluoroacetate.

Alternatively named: 1,1'-(*m*-Dimethylenebenzene)-N^4, $N^{4'}$-(hexane-1,6-diyl)-bis-(4-aminoquinolinium) di-trifluoroacetate:

N^4, $N^{4'}$-(Hexane-1,6-diyl)-bis-(4-aminoquinoline) (0.5 g, 1.35 mmol) and 1,3-di-(bromomethyl)benzene (0.36 g, 1.35 mmol) in 2-butanone (85 ml) were heated under reflux with stirring for 5 days and then cooled. The resulting precipitate was collected, washed extensively with diethyl ether, and purified by preparative HPLC to give the product as a crystalline solid which was dried in vacuo at 40 °C for 3 days and had mp: 228-230 °C. Analysis for $C_{32}H_{32}N_4$, 2.3 CF_3COOH. Calculated:C, 59.82, H, 4.70; N, 7.62%. Found: C, 59.52, H, 4.73; N, 7.59%.

Compound 38

6,12-Diaza-3(1,3)-benzena-1,5(1,4)-diquinolinacyclododecaphane di-trifluoroacetate.

Alternatively named: 1,1'-(*m*-Dimethylenebenzene)-N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinolinium) di-trifluoroacetate:

This was prepared similarly to Compound 37 from N^4, $N^{4'}$-(pentane-1,5-diyl)-bis-(4-aminoquinoline) and 1,3-di-

(bromomethyl)benzene and obtained as a white crystalline powder, mp: 238-240 °C. Analysis for $C_{31}H_{30}N_4$, 2.2 CF_3COOH. Calculated: C, 59.93, H, 4.57; N, 7.90%. Found: C, 59.91, H, 4.54; N, 7.99%.

Compound 39

6,11-Diaza-3(1,3)-benzena-1,5(1,4)-diquinolinacycloundecaphane di-trifluoroacetate.

Alternatively named: **1,1'-(*m*-Dimethylenebenzene)-N^4, $N^{4'}$-(butane-1,4-diyl)-bis-(4-aminoquinolinium) di-trifluoroacetate:**

This was prepared similarly to Compound 37 from N^4, $N^{4'}$-(butane-1,4-diyl)-bis-(4-aminoquinoline) and 1,3-di-(bromomethyl)benzene and obtained as a white crystalline solid, mp: 220-222 °C. Analysis for $C_{30}H_{28}N_4$, 2.6 CF_3COOH. Calculated: C, 57.05, H, 4.16; N, 7.56%. Found: C, 57.04, H, 4.26; N, 7.61%

Compound 40

6,10-Diaza-3(1,3)-benzena-1,5(1,4)-diquinolinacyclodecaphane tri-trifluoroacetate.

Alternatively named: **1,1'-(*m*-Dimethylenebenzene)-N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-aminoquinolinium) tri-trifluoroacetate:**

This was prepared similarly to Compound 37 from N^4, $N^{4'}$-(propane-1,3-diyl)-bis-(4-aminoquinoline) and 1,3-di-

(bromomethyl)benzene and obtained as a white crystalline solid, mp: 191-193 °C. Analysis for $C_{29}H_{26}N_4$, 3 CF_3COOH. Calculated: C, 54.41, H, 3.78; N, 7.25%. Found: C, 54.57, H, 3.56; N, 7.19%.

Compound 41

8,15-Diaza-1,7(1,4)-diquinolinacyclopentadecaphane di-trifluoroacetate. Alternatively named: 1,1'-(Pentane-1,5-diyl)-N^4, $N^{4'}$-(hexane-1,6-diyl)-bis-(4-aminoquinolinium) di-trifluoroacetate:

This was similarly prepared from N^4, $N^{4'}$-(hexane-1,6-diyl)-bis-(4-aminoquinoline) and 1,5-diiodopentane and obtained as a white crystalline solid, mp: 216-218 °C. Analysis for $C_{29}H_{34}N_4$, 2.2 CF_3COOH. Calculated: C, 58.19, H, 5.29; N, 8.13%. Found: C, 58.40, H, 5.41; N, 8.24%.

In order to test the potency of these compounds as SK_{Ca} channel blockers, the following method was used.

Preparation of cultured sympathetic neurones

Seventeen-day old Sprague Dawley rats were killed by inhalation of a rising concentration of CO_2, and the superior cervical ganglia were removed. The ganglia were de-sheathed, cut into small pieces and incubated in Ca^{2+} and Mg^{2+} free Hanks's balanced salt solution (Gibco) containing 370 U ml^{-1} collagenase and 6 mg ml^{-1} bovine serum albumin at 37°C for 15 min. This was followed by incubation in Hanks's balanced salt solution containing 1 mg ml^{-1} trypsin and 6 mg ml^{-1} bovine serum albumin for 30 min. Ganglia were then dissociated using a fire-polished Pasteur pipette, and the resultant cell suspension plated onto laminin coated plastic culture dishes. Cells were grown in L-15 medium supplemented with 10% foetal calf serum, 0.2 mM glutamine, 0.6%(w/v) D-glucose, 0.19%(w/v) $NaHCO_3$, penicillin (100 U ml^{-1}), streptomycin (100 μg ml^{-1}) and nerve growth factor (mouse submaxillary gland 50 ng ml^{-1}). Cells were maintained at 37°C in an atmosphere of 95% O_2:5% CO_2 and are used between 6 hours and 10 days in culture.

Inhibition of the afterhyperpolarisation (AHP) of cultured sympathetic neurones

Recording the AHP which follows the action potential in sympathetic neurones provides a indirect relatively simple and convenient means of testing compounds for their ability to block neuronal SK_{Ca} channels.

A culture dish was perfused with a solution (hereafter referred to as normal physiological solution) of the following composition (mM): NaCl 154; KCl 4.7; $CaCl_2$ 2.5; $MgCl_2$ 1.2; glucose 5.6; HEPES 10 (HEPES is N-(2-hydroxyethyl) piperazine-N'-(2-ethane sulfonic acid); adjusted to pH 7.4 with NaOH. Intracellular recordings were made using conventional 'sharp' micro-electrodes filled with 1 M KCl (resistance 80-120 MΩ) connected to the headstage of a Neurolog NL102 amplifier. Action potentials were evoked by injection of a 30 ms depolarizing current pulse every 5 s. The test compounds as synthesised in the example above were applied by bath perfusion for long enough (1-3 min) to cause a steady reduction in the AHP. The extent of the inhibition is expressed as a percentage.

The results are then summarised as an IC_{50} value, i.e. the concentration of compound required to produce an

inhibition of 50%; this is determined by iterative curve fitting and has an associated standard deviation (s.d.).

Dequalinium has previously shown to be a potent and selective inhibitor of the AHP in sympathetic neurones, with an IC_{50} of 1 μM [Dunn, P.M (1994. Dequalinium, a selective blocker of the slow afterhyperpolarization in rat sympathetic neurones in culture. European Journal of Pharmacology, 252, 189-194]. In the present study it was slightly more effective with an average IC_{50} of 0.60 ± 0.05 μM (fitted value ± s.d. data from 17 cells), and dequalinium was used in each test as an internal standard. Compound A was found to be considerably more active than dequalinium with an IC_{50} of 0.08 ± 0.02 μM (fitted value ± s.d. data from 12 cells). Gallamine is over 100 times less potent than dequalinium, with an IC_{50} of 68.0 ± 8.4 μM (fitted value ± s.d. data from 5 cells).

The results of the tests are shown in Table 2 below. In this table, the biological activity of each compound is expressed as an IC50 (μM) These values were determined by iterative curve fitting and are given with the approximate standard deviation of the fitted value. The use of dequalinium as a reference compound

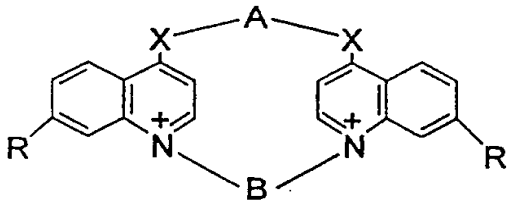
provides a means of standardising assays carried out at different times, and with preparations of varying sensitivity. This measure of potency is used when relating the biological activity of the new compounds to their chemical structure. A number of compounds show a higher potency than Compound A.

Table 2

Compound	IC_{50} (μM)	s.d.
1	0.166	0.03
2	0.11	0.005
3	0.092	0.05
4	0.18	0.04
5	0.15	0.01
6	0.21	0.02
7	0.43	0.07
8	0.13	0.01
9	0.07	0.01
10	0.003	0.0003
11	0.06	0.004
12	0.1	0.01
13	0.025	0.008
14	0.028	0.003
15	0.26	0.04
16	0.15	0.03
17	0.25	0.1
18	0.38	0.05
19	0.28	0.01
20	0.12	0.05
21	0.19	0.02
22	0.26	0.005
23	0.06	0.006
24	0.002	0.0005
25	0.015	0.003
26	0.016	0.004
27	0.04	0.005
28	0.009	0.004
29	0.03	0.006
30	0.13	0.06
31	0.38	0.001
32	0.63	0.02
33	0.06	0.003
34	0.15	0.02
35	0.065	0.009
36	0.15	0.06
37	0.035	0.007

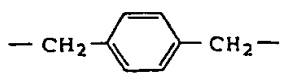
38	0.031	0.001
39	0.01	0.001
41	0.012	0.002

Compounds of the invention 42 to 57 made as described below have the structures given by the following structural formula V and Table 3:-

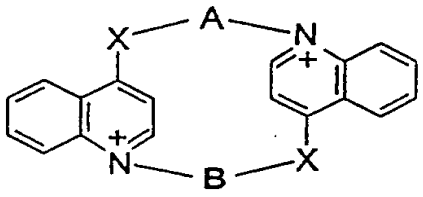


V

Table 3

Compound	R	A	B	X
42	H	$CH_2CH_2SCH_2CH_2$	$CH_2CH_2OCH_2CH_2$	NH
43	H	$CH_2CH_2OCH_2CH_2$	$CH_2CH_2OCH_2CH_2$	NH
44	H	$CH_2CH_2OCH_2CH_2$	$(CH_2)_5$	NH
45	H	$CH_2CH_2OCH_2CH_2$	$CH_2CH_2SCH_2CH_2$	NH
46	H	$(CH_2)_5$	$CH_2CH_2OCH_2CH_2$	NH
47	H	$CH_2CH_2SCH_2CH_2$	$(CH_2)_5$	NH
48	H	$(CH_2)_5$	$CH_2CH_2SCH_2CH_2$	NH
49	H	$CH_2CH_2SCH_2CH_2$	$CH_2CH_2SCH_2CH_2$	NH
50	H	$(CH_2)_5$	$(CH_2)_5$	N-CH_3
51	H	$(CH_2)_5$	$(CH_2)_5$	N-benzyl
52	H	$(CH_2)_5$	$(CH_2)_5$	S
53	CF_3	$(CH_2)_5$	$(CH_2)_5$	NH
54	Cl	$(CH_2)_5$	$(CH_2)_5$	NH
55	H	$(CH_2)_5$	$CH{=}C{=}CHCH_2$	NH
56	H	$(CH_2)_5$		NH
57	H	$CH_2C{\equiv}CCH_2$	$(CH_2)_5$	NH

Compounds of the invention 58 to 62 also described below have the structures given by the following structural formula VI and Table 4:-

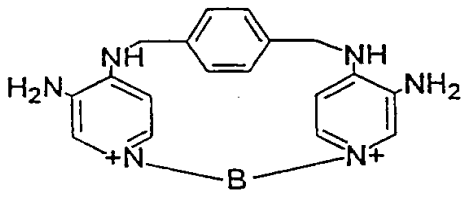


VI

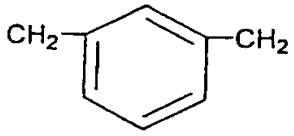
Table 4

Compound	A	B	X
58	$(CH_2)_6$	$(CH_2)_6$	NH
59	$(CH_2)_5$	$(CH_2)_5$	NH
60	$(CH_2)_5$	$(CH_2)_5$	N-CH_3
61	$(CH_2)_5$	$(CH_2)_5$	N-benzyl
62	$(CH_2)_6$	$(CH_2)_6$	N-benzyl

Compounds of the invention 63 and 64 described below have the structures given by the following structural formula VII:



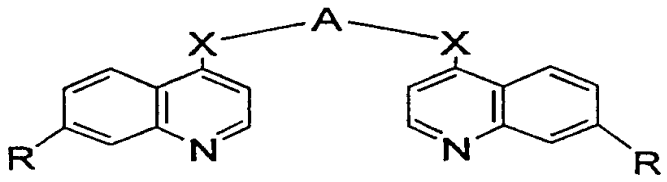
VII

In Compound 63 B is 

and

in Compound 64 B is $(CH_2)_5$.

Intermediates VII to XII have the structural formula:

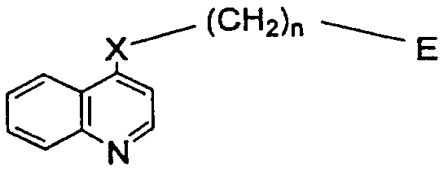


wherein A, R and X are given in Table 5

Table 5

Intermediates	R	A	X
VII	H	$CH_2CH_2SCH_2CH_2$	NH
VIII	H	$CH_2CH_2OCH_2CH_2$	NH
IX	H	$(CH_2)_5$	N-CH_3
X	H	$(CH_2)_5$	N-benzyl
XI	H	$(CH_2)_5$	S
XII	CF_3	$(CH_2)_5$	NH

Intermediates XIII, XIV, XVIII, XIX, XX have the structural formula:



wherein E, n and X are given in Table 6

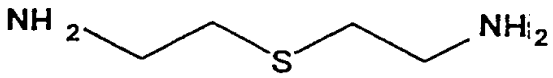
Table 6

Intermediates	E	n	X
XIII	I	$(CH_2)_5$	NH
XIV	I	$(CH_2)_6$	NH
XVIII	I	$(CH_2)_5$	N-CH_3
XIX	I	$(CH_2)_5$	N-benzyl
XX	I	$(CH_2)_6$	N-benzyl

Next, we describe the preparation of some starting materials and of Intermediates VII to XVII which were themselves used in the synthesis of Compounds 42 to 62 of the invention.

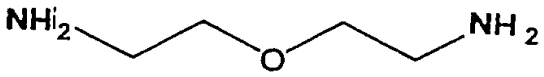
The following known compounds were prepared as starting materials by the method given in respective reference given for each

A. Gabriel; Chem. Ber.: 1981, 24, 1114



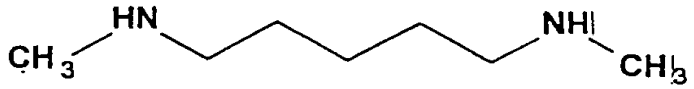
bis(2-aminoethyl) sulfide

B. Anikin, V.F.; et. al; Chem. Heterocycl. Compd. (Engl. Transl.) 1982, 18, 193-196



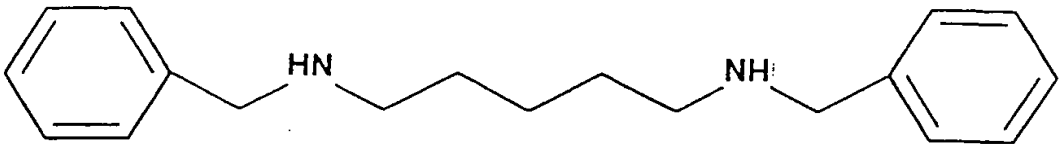
bis(2-aminoethyl) ether

C. Devinsky, F.; et. al; Synthesis; 1980, 4, 303-305



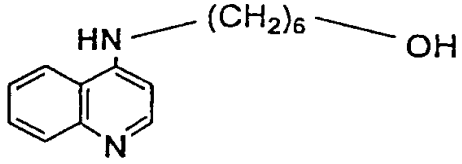
N,N'-dimethyl-pentane-1,5-diamine

D. Lee, W.W.; et al; J. Med. Chem.; 1963, 6, 567-569



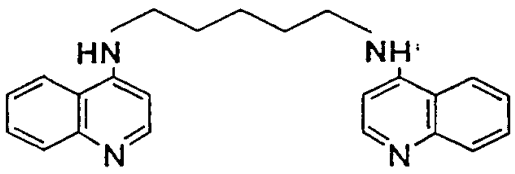
N,N'-dibenzyl-pentane-1,5-diamine

E. Sandoz-Wander, Inc., USA; Division of U.S. Patent 3,856,796 (CA 1963,85: 108554)



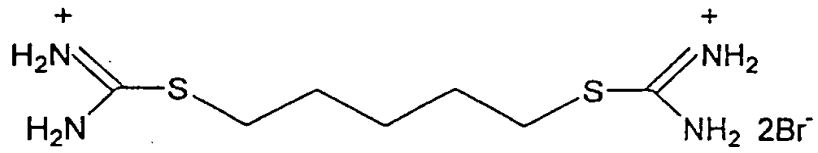
6-(4-quinolinyl)aminohexan-1-ol

F. Adams,A. et al; Eur. J. Pharmacol. 1986, 127, 27-35



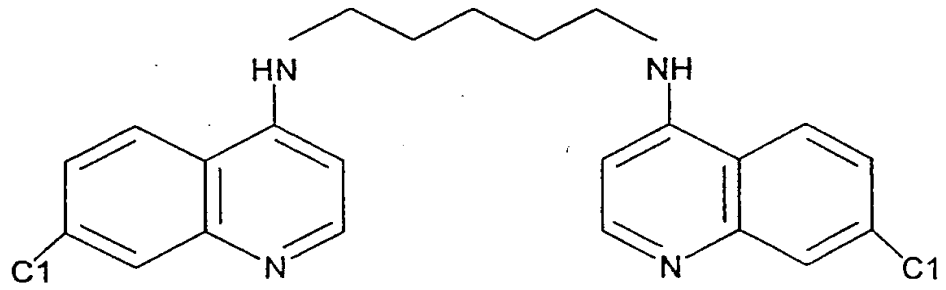
N,N'-Bis(4-quinolinyl)pentane-1,5-diamine

G. Grogan,G C.H. et al; J. Org. Chem. 1953, *18*, 728-735



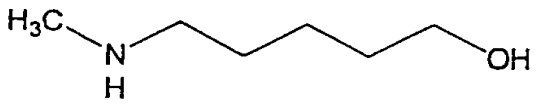
Pentan-1,5-diisothiuronium dibromide

H. Vennerstrom, J.L. et al; J. Med. Chem. 1992, *35*, 2119-2134



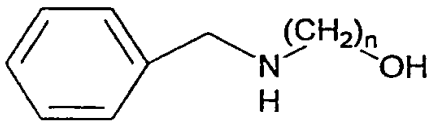
N,N'-Bis(7-chloroquinolin-4-yl)pentane-1,5-diamine

I. Scriabine; Bull. SOc. Chim. Fr. 1947, 455



5-methylaminopentan-1-ol

J. Eliel; et al; J. Org. Chem. 1965, *30*, 2450-2451



5-benzylaminopentan-1-ol

6-benzylaminohexan-1-ol

Intermediate VII

Bis[2-(4-quinolinyl)aminoethyl] sulfide,

A mixture of bis(2-aminoethyl) sulfide (starting material A)(2.2 g, 18 mmol) and 4-chloroquinoline (5.9 g, 36 mmol) in pentanol (100 ml) was heated at reflux for 10 h, the cooled and the precipitate was collected by filtration and washed with diethyl ether. The filtration cake was dissolved in hot methanol, basified with 1N NaOH solution to pH > 9. After cooling, the precipitate was collected by filtration, washed with water and acetone to give an off-white solid, mp: 148°C.

Analysis for $C_{22}H_{22}N_4S$, 0.3 H_2O:

Calculated: C, 69.55; H, 6.00; N, 14.75%.

Found: C, 69.61; H, 6.07; N, 14.68%.

Intermediate VIII

Bis[2-(4-quinolinyl)aminoethyl] ether:

A mixture of bis-(2-aminoethyl) ether (starting material B) (1.37 g, 13 mmol) and 4-chloroquinoline (4.3 g, 26 mmol) in pentanol (100 ml) was heated at reflux for 10 h. After cooling, the precipitate was collected by filtration. It was then shaken with 1N NaOH aqueous solution and dichloromethane. The organic phase was dried over Na_2SO_4 and evaporated in vacuum to

dryness. The residue was crystallised from ethyl acetate to give an off white solid, mp: 182°C.

Intermediate IX

N,N'-Bis(4-quinolinyl)-N,N'-dimethylpentane-1,5-diamine:

A mixture of N,N'-dimethyl-pentane-1,5-diamine (starting material C) (1.0 g, 7 mmol) and 4-chloroquinoline (2.52 g, 15 mmol) in pentanol (20 ml) was heated at reflux for 24 h. After cooling, diethyl ether was added and the precipitate was collected by filtration. The obtained filtration cake was dissolved in hot methanol, basified with 1N NaOH solution to pH> 9. A precipitate was formed and it was collected by filtration, washed with water and acetone to give an off-white solid.

Intermediate X

N,N'-Bis(4-quinolinyl)-N,N'-dibenzylpentane-1,5-diamine:

To a mixture of 4-hydroxyquinoline (1.9 g, 13 mmol) and pyridine (1.0 g, 13 mmol) in CH_2Cl_2 (20 ml) was added dropwise trifluoromethanesulfonic anhydride at 0 °C. The reaction mixture was stirred at room temperature

for 30 min. The precipitate was filtered off and the filtrate was concentrated in vacuum. The obtained residue (1.7 g, 6.1 mmol) and N,N'-dibenzyl-pentane-1,5-diamine (starting material D)(0.8 g, 2.8 mmol) were dissolved in 2-methoxyethyl ether (20 ml) and was heated at 100 °C for 5 h. After cooling, the reaction mixture was purified by chromatography over a silica gel column using a mixture of CH_2Cl_2/MeOH/NH_4OH (20/1/0.1) as eluant to give a pale yellow product.

Intermediate XI

1,5-Bis(quinolin-4-ylthio)-pentane:

A mixture of S,S'-(pentan-1,5-yl)-diisothiuronium dibromide (starting material G)(1.32 g, 3.45 mmol), 4-chloroquinoline (1.13 g, 6.9 mmol) and KOH (0.8 g, 14.0 mmol) in absolute EtOH was heated at reflux for 3 h. The solvent was evaporated and the residue was dispersed in water, extracted with CH_2Cl_2. The combined extracts were dried over K_2CO_3. Evaporation of the solvents gave a off-white solid, mp: 107 °C.

Intermediate XII

N,N'-Bis(7-trifluoroquinolin-4-yl)pentane-1,5-diamine:

A mixture of 1,5-diaminopentane (0.51 g, 5 mmol) and 4-

chloro-7-trifluoroquinoline (2.32 g, 10 mmol) in phenol (5 g) was heated at 150 °C for 3 h, then cooled and the product was precipitated by diethyl ether. The precipitate was collected by filtration. It was then dissolved in hot methanol, basified with 1N NaOH solution to pH > 9. The resulting precipitate was collected by filtration, washed with water and acetone to give an off-white solid, mp: 290°C.

Intermediate XIII

5-Iodo-N-(4-quinolinyl)-pentylamine:

A mixture of 5-(4-quinolinyl)aminopentan-1-ol (0.4 g, 1.7 mmol) and HI (6 ml, 57%) was heated at reflux for 2 h. After cooling, the reaction mixture was diluted by water and the aqueous layer was decanted and rejected. The residue was shaken with CH_2Cl_2 and aqueous Na_2CO_3. The organic phase was washed with $Na_2S_2O_3$ solution, dried over Na_2SO_4 and evaporated in vacuum to give a white solid.

Intermediate XIV

6-Iodo-N-(4-quinolinyl)-hexylamine:

A mixture of 6-(4-quinolinyl)aminohexan-1-ol (starting material E)(1.3 g, 5.3 mmol) and HI (2 ml, 57%) was

heated at reflux for 2 h. After cooling, the reaction mixture was diluted with water and the aqueous layer was decanted and rejected. The residue was shaken with CH_2Cl_2 and aqueous Na_2CO_3. The organic phase was washed with water, dried over Na_2SO_4 and evaporated in vacuum to give a white solid.

Intermediate XV

N-Methyl-N-(4-quinolinyl)-5-aminopentan-1-ol;

A mixture of 5-methylaminopentan-1-ol (starting material I) (0.9 g, 7.7 mmol) and 4-chloroquinoline (1.0 g, 6.1 mmol) was stirred at 150°C for 4 h. After cooling, the residue was shaken with CH_2Cl_2 and aqueous Na_2CO_3. The organic layer was dried and evaporated to give the product as a gummy residue.

Intermediate XVI

N-Benzyl-N-(4-quinolinyl)-5-aminopentan-1-ol;

A mixture of 5-benzylaminopentan-1-ol (starting material J) (1.7 g, 8.8 mmol) and 4-chloroquinoline (1.0 g, 6.1 mmol) was stirred at 150°C for 4 h. Work-up as described for the preparation of intermediate XV gave intermediate XVI as gummy residue.

Intermediate XVII

N-Benzyl-N-(4-quinolinyl)-6-aminohexan-1-ol;

A mixture of 5-benzylaminohexan-1-ol (starting material J) (1.26 g, 6.1 mmol) and 4-chloroquinoline (1.0 g, 6.1 mmol) was heated at 150°C for 3 h. Work-up as described for the preparation of intermediate XV gave intermediate XVI as a gummy residue.

Intermediate XVIII

5-Iodo-N-methyl-N-(4-quinolinyl)-pentylamine:

To a stirred solution of triphenylphosphine (1.57 g, 6.0 mmol) in toluene (50 ml) was added dropwise a solution of iodine (1.52 g, 6.0 mmol) in toluene (50 ml) at room temperature, then a solution of N-methyl-N-(4-quinolinyl)-5-aminopentan-1-ol (intermediate XV) and triethylamine (0.61 g, 6.0 mmol) was added. The mixture was stirred at room temperature for 3 h. The precipitate was filtered off and the filtrate was chromatographed on a column of silica gel using diethyl ether as eluant. Evaporation of solvents afforded intermediate XVIII as a pale yellow gummy residue.

Intermediate XIX

5-Iodo-N-benzyl-N-(4-quinolinyl)-pentylamine:

This was prepared by the same procedure as that described for the preparation of intermediate XVIII, using intermediate XVI.

Intermediate XX

6-Iodo-N-benzyl-N-(4-quinolinyl)-hexylamine:
This was prepared by the same procedure as that described for the preparation of intermediate XVIII, using intermediate XVIII.

In the following syntheses, where preparative high performance liquid chromatography (HPLC) was used, it was carried out with a Gilson apparatus using a UV detector and a Kromasil C18 5 μm column. Solvent mixtures of water + 0.1% trifluoroacetic acid (TFA) and methanol + 0.1% TFA were used with a flow 18 ml/min. In many cases, some excess TFA and H_2O were retained in the salts after HPLC.

Compound 42

8,14-Diaza-1,7(1,4)-diquinolina-4-oxa-11-thiacyclotetradecaphanium dibromide sesquihydrate. Alternatively named: **1,1'-[1,5-(3-oxapentan)-diyl]-N,N'-[1,5-(3-**

thiopentan)-diyl]-bis(4-aminoquinolinium) dibromide sesquihydrate:

Bis[2-(4-quinolinyl)aminoethyl] sulfide (Intermediate VII) (0.75 g, 2.0 mmol) was dissolved in dimethyl formamide (150 ml) at room temperature and bis(2-bromoethyl) ether (0.46 g, 2.0 mmol) added. The mixture was heated at reflux for 48 h. The solvent was then evaporated in vacuum. The residue was crystallised from methanol to give an off-white solid, mp: 307°C dec.

Analysis for $C_{26}H_{30}Br_2N_4OS$, 1.5 H_2O:

Calculated: C, 49.30; H, 5.25; N, 8.84%.

Found: C, 49.23; H, 5.53; N, 8.84%.

Compound 43

8,14-Diaza-4,11-dioxa-1,7(1,4)-diquinolinacyclotetradecaphanium dibromide dihydrate. Alternatively named: **N,N'-[1,5-(3-oxapentan)-diyl]-1,1'-[1,5-(3-oxapentan)-diyl]-bis(4-aminoquinolinium) dibromide dihydrate**

Bis[2-(4-quinolinyl)aminoethyl] ether (Intermediate VIII) (0.36 g, 1.0 mmol) was dissolved in dimethyl formamide (150 ml) at room temperature and bis(2-bromoethyl) ether (0.23 g, 1.0 mmol) added. The mixture

was heated at reflux for 60 h. The solvent was then evaporated in vacuum. The residue was crystallised from methanol to give an off-white solid, mp: 324°C.

Analysis for $C_{26}H_{30}Br_2N_4O_2$, 2 H_2O:

Calculated: C, 49.86; H, 5.47; N, 8.94%.

Found: C, 50.17; H, 5.31; N, 8.99%.

Compound 44

8,14-Diaza-11-oxa-1,7(1,4)-diquinolinacyclotetradecaphanium diiodide. Alternatively named: N,N'-[1,5-(3-oxapentan)-diyl]-1,1'-(1,5-pentan-diyl)-bis(4-aminoquinolinium) diiodide

Bis[2-(4-quinolinyl)aminoethyl] ether (Intermediate VIII) (0.36 g, 1.0 mmol) was dissolved in dimethyl formamide (150 ml) at room temperature and 1,5-diiodopentane (0.32 g, 1.0 mmol) added. The mixture was heated at reflux for 96 h. The solvent was then evaporated in vacuum. The residue was crystallised from methanol and recrystallised from dimethyl formamide to give a white solid, mp: 311°C.

Analysis for $C_{27}H_{32}I_2N_4O$, 0.4 HI:

Calculated: C, 44.21; H, 4.45; N, 7.64%.

Found: C, 44.39; H, 4.52; N, 7.56%.

Compound 45

8,14-Diaza-11-oxa-1,7(1,4)-diquinolina-4-thiacyclotetra-decaphanium di-trifluoroacetate.

Alternatively named: N,N'-[1,5-(3-oxapentan)-diyl]-1,1'-[1,5-(3-thiopentan)-diyl]-bis(4-aminoquinolinium) di-trifluoroacetate:

Bis[2-(4-quinolinyl)aminoethyl] ether (Intermediate VIII) (0.36 g, 1.0 mmol) was dissolved in dimethyl formamide (150 ml) with heating and bis(2-bromoethyl) sulfide (0.25 g, 1.0 mmol) added. The mixture was heated at reflux for 4 days and then the solvent was evaporated in vacuum. The residue was purified by preparative HPLC to give a pale yellow solid, mp: 225°C dec.

Analysis for $C_{26}H_{30}N_4OS^{2+}2CF_3CO_2^-$, 0.5 CF_3CO_2H:

Calculated: C, 51.03; H, 4.21; N, 7.68%.

Found: C, 51.01; H, 4.23; N, 7.97%.

Compound 46

8,14-Diaza-4-oxa-1,7(1,4)-diquinolinacyclotetradeca-phanium dibromide dihydrate. Alternatively named: 1,1'-[1,5-(3-oxapentan)-diyl]-N,N'-(1,5-pentan-diyl)-bis-(4-aminoquinolinium) dibromide dihydrate

N,N'-Bis(4-quinolinyl)pentane-1,5-diamine (starting material F) (0.36 g, 1.0 mmol) was dissolved in dimethyl

formamide (150 ml) at room temperature and bis(2-bromoethyl) ether (0.23 g, 1.0 mmol) added. The mixture was heated to 100°C for 48 h then to reflux for 72 h. The solvent was evaporated in vacuum. The residue was crystallised from iso-propanol then recrystallised from methanol to give an off-white solid, mp: 305°C dec.

Analysis for $C_{27}H_{32}Br_2N_4O$, 2 H_2O:

Calculated: C, 51.94; H, 5.81; N, 8.97%.

Found: C, 51.98; H, 5.71; N, 9.02%.

Compound 47

8,14-Diaza-1,7(1,4)-diquinolina-11-thiacyclotetradecaphanium diiodide. Alternatively named: 1,1'-(1,5-pentan-diyl)-N,N'-[1,5-(3-thiapentan)-diyl]-bis-(4-aminoquinolinium) diiodide

Bis[2-(4-quinolinyl)aminoethyl] sulfide (Intermediate VII) (0.37 g, 1.0 mmol) was dissolved in 4-methyl-2-pentanol (150 ml) with heating and 1,5-diiodopentane (0.32 g, 1.0 mmol) added. The mixture was heated at reflux for 7 days, then cooled and the precipitate was collected by filtration. Repeated crystallisation from dimethyl formamide/methanol gave a white solid, mp: 290 °C dec.

Analysis for $C_{27}H_{32}I_2N_4S$, 0.2 HI:

Calculated: C, 51.03; H, 4.21; N, 7.68%.

Found: C, 51.01; H, 4.23; N, 7.97%.

Compound 48

8,14-Diaza-1,7(1,4)-diquinolina-4-thiacyclotetradecaphanium di-trifluoroacetate hemihydrate. Alternatively named: N,N'-(1,5-pentan-diyl)-1,1'-[1,5-(3-thiapentan)-diyl]-bis-(4-aminoquinolinium) di-trifluoroacetate hemihydrate

N,N'-Bis(4-quinolinyl)pentane-1,5-diamine (starting material F) (0.50 g, 1.4 mmol) was dissolved in a mixture of 2-butanone (100 ml) and dimethyl formamide (30 ml) with heating and bis(2-bromoethyl) sulfide (0.35 g, 1.4 mmol) added. The mixture was heated at reflux for 6 days, then cooled and the precipitate was collected by filtration. The crude product was purified by preparative HPLC to give a pale yellow solid, mp: 203°C dec.

Analysis for $C_{27}H_{32}N_4S^{2+}2CF_3CO_2^-$, 0.5 H_2O, 0.5 CF_3CO_2H:
Calculated: C, 52.17; H, 4.58; N, 7.61%.
Found: C, 52.03; H, 4.94; N, 7.93%.

Compound 49

8,14-Diaza-1,7(1,4)-diquinolina-4,11-dithiacyclotetradecaphanium di-trifluoroacetate. Alternatively

named: N,N'-[1,5-(3-thiapentan)-diyl]-1,1'-[1,5-(3-thiapentan)-diyl]-bis-(4-aminoquinolinium) di-trifluoroacetate

Bis[2-(4-quinolinyl)aminoethyl] sulfide (Intermediate VII) (0.74 g, 2.0 mmol) was dissolved in a mixture of 2-butanone (100 ml) and dimethyl formamide (30 ml) with heating and bis(2-bromoethyl) sulfide (0.50 g, 2.0 mmol) added. The mixture was heated at reflux for 5 days and a precipitate was formed. After cooling, the precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 212°C dec.

Analysis for $C_{26}H_{30}N_4S_2^{2+}2CF_3CO_2^-$, 0.5 CF_3CO_2H:

Calculated: C, 49.93; H, 4.12; N, 7.51%.

Found: C, 49.28; H, 4.31; N, 7.86%.

Compound 50

8,14-Diaza-8,14-dimethyl-1,7(1,4)-diquinolinacyclotetradecaphanium di-trifluoroacetate trihydrate.

Alternatively named: N,N'-dimethyl-N,N'-(1,5-pentan-diyl)-1,1'-(1,5-pentan-diyl)-bis(4-aminoquinolinium) di-trifluoroacetate trihydrate

N,N'-Bis(4-quinolinyl)-N,N'-dimethyl-pentane-1,5-diamine, (Intermediate IX) (1.7 g, 4.3 mmol) was dissolved in 2-butanone (200 ml) and 1,5-diiodopentane

(1.4 g, 4.3 mmol) added. The mixture was heated at reflux for 7 days. It was cooled and the resulting precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 125°C.

Analysis for $C_{30}H_{38}N_4^{2+}2CF_3CO_2^-$, 0.8 CF_3CO_2H, $3H_2O$:

Calculated: C, 51.77; H, 5.47; N, 6.78%.

Found: C, 51.87; H, 5.17; N, 6.71%.

Compound 51

8,14-Diaza-8,14-dibenzyl-1,7(1,4)-diquinolinacyclotetradecaphanium di-trifluoroacetate monohydrate.

Alternatively named: N,N'-dibenzyl-N,N'-(1,5-pentandiyl)-1,1'-(1,5-pentan-diyl)-bis(4-aminoquinolinium) di-trifluoroacetate monohydrate

N,N'-Bis(4-quinolinyl)-N,N'-dibenzylpentane-1,5-diamine (Intermediate X) (0.6 g, 1.1 mmol) was dissolved in 2-butanone (100 ml) and 1,5-diiodopentane (0.50 g, 1.5 mmol) added. The mixture was heated at reflux for 48 h. After removing half of the solvent, the mixture was heated at reflux for a further 24 h. It was cooled, the resulting precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 110°C.

Analysis for $C_{42}H_{46}N_4^{2+}2CF_3CO_2^-$, 1.8 CF_3CO_2H, $1H_2O$:

Calculated: C, 56.41; H, 4.75; N, 5.30%.

Found: C, 56.46; H, 4.86; N, 5.40%.

Compound 52

1,7(1,4)-Diquinolina-8,14-dithiacyclotetradecaphanium di-trifluoroacetate. Alternatively named: S,S'-(1,5-pentan-diyl)-1,1'-(1,5-pentan-diyl)-bis(4-thioquinolinium) di-trifluoroacetate

S,S'-(1,5-Pentan-diyl)-bis(4-thiaquinoline) (Intermediate XI) (0.7 g, 1.8 mmol) was dissolved in 2-butanone (80 ml) and 1,5-diiodopentane (0.87 g, 2.6 mmol) added. The mixture was heated at reflux for 4 days. It was cooled and the resulting precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 182°C.

Analysis for $C_{28}H_{32}N_2S_2^{2+}2CF_3CO_2^-$, 0.3 CF_3CO_2H:

Calculated: C, 54.31; H, 4.52; N, 3.89%.

Found: C, 54.25; H, 4.61; N, 3.85%.

Compound 53

8,14-Diaza-1^7,7^7-ditrifluoromethyl-1,7(1,4)-diquinolinacyclotetradecaphanium di-trifluoroacetate. Alternatively named: N,N'-(1,5-pentan-diyl)-1,1'-(1,5-pentan-diyl)-bis(4-amino-7-trifluoromethylquinolinium)

di-trifluoroacetate

N,N'-Bis(7-trifluoromethylquinolin-4-yl)pentane-1,5-diamine, (Intermediate XII) (0.49 g, 1.0 mmol) was dissolved in 2-butanone (100 ml) and 1,5-diiodopentane (0.49 g, 1.5 mmol) added. The mixture was heated at reflux for 3 days. It was cooled, the resulting precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 234°C.

Analysis for $C_{30}H_{32}N_4^{2+}2CF_3CO_2^-$, 0.2 CF_3CO_2H:

Calculated: C, 50.92; H, 4.00; N, 6.9%.

Found: C, 51.08; H, 3.84; N, 6.66%.

Compound 54

8,14-Diaza-1^7,7^7-dichloro-1,7(1,4)-diquinolinacyclotetradecaphanium di-trifluoroacetate sesquihydrate.

Alternatively named: N,N'-(1,5-pentan-diyl)-1,1'-(1,5-pentan-diyl)-bis(4-amino-7-chloroquinolinium) di-trifluoroacetate sesquihydrate

N,N'-Bis(7-chloroquinolin-4-yl)pentane-1,5-diamine (starting material H) (0.43 g, 1.0 mmol) was dissolved in dimethyl formamide (80 ml) and 1,5-diiodopentane (0.49 g, 1.5 mmol) added. The mixture was heated at 100 °C for 48 h. It was cooled, the resulting precipitate was collected by filtration and purified by preparative

HPLC to give a pale yellow solid, mp: 232°C (dec).

Analysis for $C_{28}H_{32}Cl_2N_4^{2+}2CF_3CO_2^-$, 0.9 CF_3CO_2H, 1.5 H_2O:

Calculated: C, 47.70; H, 4.25; N, 6.58%.

Found: C, 47.76; H, 4.23; N, 6.66%.

Compound 55

7,13-Diaza-2,3-diene-1,6(1,4)-diquinolinacyclotrideca-phanium di-trifluoroacetate. Alternatively named: N,N'-(butan-1,2-diene-1,4-diyl)-1,1'-(1,5-pentan-diyl)-bis(4-aminoquinolinium) di-trifluoroacetate

N,N'-Bis(4-quinolinyl)pentane-1,5-diamine (starting material F) (0.35 g, 1.0 mmol) was dissolved in 2-butanone (100 ml) and 1,4-dichloro-2-butyne (0.12 g, 1.0 mmol) added. The mixture was heated at reflux for 5 days. It was cooled, the resulting precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 150°C (dec).

Analysis for $C_{27}H_{28}N_4^{2+}2CF_3CO_2^-$, 0.6 CF_3CO_2H:

Calculated: C, 55.02; H, 4.1; N, 7.97%.

Found: C, 55.14; H, 4.35; N, 7.83%.

Compound 56

6,12-Diaza-3(1,4)-benza-1,5(1,4)-di-quinolinacyclododeca-phanium di-trifluoroacetate hemi-

hydrate. Alternatively named: 1,1'-(*p*-xylylene)-N,N'-(1,5-pentan-diyl)-bis(4-aminoquinolinium) di-trifluoroacetate hemihydrate

N,N'-Bis(4-quinolinyl)pentane-1,5-diamine (starting material F)(0.43 g, 1.0 mmol) was dissolved in a mixture of 2-butanone (50 ml) and dimethyl formamide (10 ml) and α,α'-dibromo-p-xylene (0.4 g, 1.5 mmol) added. The mixture was heated at reflux for 3 days. It was cooled, the resulting precipitate was collected by filtration and purified by preparative HPLC to give a white solid, mp: 220°C (dec).

Analysis for $C_{31}H_{32}Cl_2N_4^{2+}2CF_3CO_2^-$, 1.0 CF_3CO_2H, 0.5 H_2O:

Calculated: C, 54.89; H, 4.23; N, 6.92%.

Found: C, 54.60; H, 4.21; N, 6.92%.

Compound 57

8,13-Diaza-1,7(1,4)-diquinoline-10-ynecyclotridecaphanium di-trifluoroacetate.

Alternatively named: 1,1'-(1,5-pentan-diyl))-N,N'-(but-2-yne-1,4-diyl)-bis(4-aminoquinolinium) di-trifluoroacetate:

To a mixture of 4-hydroxyquinoline (2.0 g, 13.8 mmol) and pyridine (1.1 g, 14.0 mmol) in CH_2Cl_2 was added dropwise a solution of trifluoromethanesulfonic anhydride at 0°C. After addition, the reaction mixture

was stirred at room temperature for 30 min. The precipitate produced was filtered off and the filtrate was concentrated in vacuum to give a pale yellow oil. It was dissolved in 20 ml of 2-methoxyethyl ether and but-2-yne-1,4-diamine (Johnson: J. Chem. Soc. 1946; 1012) (0.25 g, 3.0 mmol) was added. The mixture was stirred at 100°C for 24 h. After cooling the precipitate generated was collected by filtration, washed with acetone to give a solid, mp : 210°C. This solid is N,N'-Bis(4-quinolinyl)-but-2-yne-1,4-diamine.

N,N'-Bis(4-quinolinyl)-but-2-yne-1,4-diamine (0.28 g, 0.83 mmol) was dissolved in a mixture of 2-butanone (50 ml) and dimethyl formamide (10 ml) with heating and 1,5-diiodopentane (0.28 g, 0.86 mmol) added. The mixture was heated at reflux for 5 days. After cooling, the precipitate produced was collected by filtration and purified by preparative HPLC to give a white solid, mp: 226°C dec.

Analysis for $C_{27}H_{28}N_4^{2+}2CF_3CO_2^-$, 0.16 CF_3CO_2H:
Calculated: C, 57.62: H, 4.35; N, 8.58%.
Found: C, 57,56; H, 4.33; N, 8.60%.

Compound 58

8,16-Diaza-1(1,4),9(4,1)-diquinolinacyclohexadecaphanium di-trifluoroacetate

dihydrate. Alternatively named: 1,N'-(1,6-hexan-diyl)-N,1'-(1,6-hexan-diyl)-bis(4-amino quinolinium) di-trifluoroacetate dihydrate

6-Iodo-N-(4-quinolinyl)-hexylamine (Intermediate XIV) (1.7 g, 4.8 mmol) was dissolved in a mixture of 2-butanone (90 ml) and dimethyl formamide (30 ml). The mixture was heated at reflux for 5 days, then cooled and the resulting precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 203°C dec.

Analysis for $C_{30}H_{38}N_4^{2+}2CF_3CO_2^-$, 0.5 CF_3CO_2H, 2 H_2O:

Calculated: C, 54.33; H, 5.54; N, 7.24%.

Found: C, 54.17; H, 5.55; N, 7.31%.

Compound 59

7,14-Diaza-1(1,4),8(4,1)-diquinolinacyclotetradecaphanium di-trifluoroacetate dihydrate. Alternatively named: 1,N'-(1,5-pentan-diyl)-N,1'-(1,5-pentan-diyl)-bis(4-amino-quinolinium) di-trifluoroacetate dihydrate

5-Iodo-N-(4-quinolinyl)-pentylamine (Intermediate XIII) (0.52 g, 1.5 mmol) was dissolved in a mixture of 2-butanone (40 ml) and dimethyl formamide (3 ml). The mixture was heated at reflux for 4 days, then cooled and the resulting precipitate was collected by

filtration and purified by preparative HPLC to give a pale yellow solid, mp: 209°C dec.

Analysis for $C_{28}H_{34}N_4^{2+}2CF_3CO_2^-$, 0.4 CF_3CO_2H, 2 H_2O:

Calculated: C, 56.42; H, 4.97; N, 8.02%.

Found: C, 56.24; H, 4.93; N, 8.00%.

Compound 60

7,14-Diaza-7,14-dimethyl-1(1,4),8(4,1)-diquinolinacyclo-tetradecaphanium di-trifluoroacetate.

Alternatively named: N,N'-dimethyl-1,N'-(1,5-pentan-diyl)-N,1'-(1,5-pentan-diyl)-bis(4-aminoquinolinium) di-trifluoro-acetate

5-Iodo-N-Methyl-N-(4-quinolinyl)-pentylamine Intermediate XVIII) (0.8 g, 2.3 mmol) was dissolved in 2-butanone (80 ml). The solution was heated at reflux for 4 days, then cooled and the resulting precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 205°C dec.

Analysis for $C_{30}H_{38}N_4^{2+}2CF_3CO_2^-$, 0.8 CF_3CO_2H:

Calculated: C, 55.39; H, 5.07; N, 7.26%.

Found: C, 55.38; H, 5.24; N, 7.37%.

Compound 61

7,14-Diaza-7,14-dibenzyl-1(1,4),8(4,1)-

diquinolinacyclo-tetradecaphanium di-trifluoroacetate.
Alternatively named: **N,N'-dibenzyl-1,N'-(1,5-pentan-diyl)-N,1'-(1,5-pentan-diyl)-bis(4-aminoquinolinium) di-trifluoroacetate**

5-Iodo-N-benzyl-N-(4-quinolinyl)-pentylamine (Intermediate XIX) (0.5 g, 1.2 mmol) was dissolved in 2-butanone (80 ml). The solution was heated at reflux for 3 days, then cooled and the resulting precipitate was collected by filtration and purified by preparative HPLC to give a pale yellow solid, mp: 145°C.
Analysis for $C_{42}H_{46}N_4^{2+}2CF_3CO_2^-$, 2 CF_3CO_2H:
Calculated: C, 56.78; H, 4.60; N, 5.35%.
Found: C, 56.61; H, 4.56; N, 5.28%.

Compound 62

8,16-Diaza-8,16-dibenzyl-1(1,4),9(4,1)-diquinolinacyclo-hexadecaphanium di-trifluoroacetate.
Alternatively named: **N,N'-dibenzyl-1,N'-(1,6-hexan-diyl)-N,1'-(1,6-hexan-diyl)-bis(4-aminoquinolinium) di-trifluoroacetate**

6-Iodo-N-benzyl-N-(4-quinolinyl)-hexylamine (Intermediate XX) (1.5 g, 3.4 mmol) was dissolved in 2-butanone (90 ml). The solution was heated at reflux for 5 days, then cooled and the resulting precipitate was collected by filtration and purified by preparative

HPLC to give a pale yellow solid, mp: 175°C dec.

Analysis for $C_{44}H_{50}N_4^{2+}2CF_3CO_2^-$, 1.3 CF_3CO_2H:

Calculated: C, 60.22; H, 5.17; N, 5.55%.

Found: C, 60.10; H, 5.14; N, 5.47%.

Compound 63

$1^3,5^3$-Diamino-6,10-diaza-3(1,3), 8(1,4)-dibenza-1,5(1,4)-dipyridinacyclodecaphanium dibromide.

Alternatively named: 1,1'-(*m*-xylylene)-N_4, N_4'-(*p*-xylylene)-bis(3,4-diaminopyridinium) dibromide

N,N'-Bis(3-aminopyridin-4-yl)-xylene-α,α'-diamine (0.12 g, 0.38 mmol) and α,α'-dibromo-*m*-xylene (0.10 g, 0.38 mmol) was dissolved with heating in pentan-1-ol (65 ml). The solution was heated at reflux for 6 days with stirring. During the course of the reaction a creamy precipitate was formed. After cooling, the solid was collected by vacuum filtration. The brown solid was washed with methanol and dried *in vacuo* (100 °C) and a hygroscopic beige solid was obtained, mp: 355°C.

Analysis for $C_{26}H_{28}N_6^{2+}2Br^-$, 0.3 $C_5H_{11}OH$, 0.5 H_2O:

Calculated: C, 53.29; H, 5.30; N, 13.56%.

Found: C, 53.19; H, 5.00; N, 13.19%.

Compound 64

$1^3,7^3$-Diamino-2,6-diaza-4(1,4)-benza-1,7(4,1)-dipyridina-cyclododecaphanium diiodide methanolate.

Alternatively named: 1,1'-(pentan-1,5-diyl)-N_4, N_4'-(*p*-xylylene)-bis(3,4-diaminopyridinium) diiodide methanolate

N,N'-Bis(3-aminopyridin-4-yl)-xylene-α,α'-diamine (0.15 g, 0.47 mmol) and 1,5-diiodopentane (0.15 g, 0.47 mmol) was dissolved with heating in pentan-1-ol (60 ml). The solution was heated at reflux for 6 days with stirring. During the course of the reaction a brown precipitate was formed. After cooling, the solid was collected by vacuum filtration. The brown solid was washed with methanol and dried *in vacuuo* (100 °C) to yield a beige solid, mp: 290°C.

Analysis for $C_{23}H_{30}N_6^{2+}2I^-$, 1.0 CH_3OH, 0.4 H_2O:

Calculated: C, 42.17; H, 5.13; N, 12.24%.

Found: C, 41.86; H, 4.80; N, 12.06%.

The biological potency of some of these compounds was assessed by their ability to reduce the amplitude of the after-hyperpolarization (AHP) recorded from rat superior cervical ganglion cells in short term tissue culture, using the technique described in detail above. The results are in Table 7

Table 7

Compound	IC_{50} (μm)	s.d.
42	0.058	0.004
43	0.017	0.002
44	0.016	0.004
45	0.038	0.006
46	0.0048	0.0004
47	0.018	0.025
48	0.0041	0.00045
49	0.042	0.009
50	0.124	0.016
51	0.15	0.025
52	0.16	0.04
53	0.01	0.001
54	0.0031	0.0003
58	0.076	0.013
59	0.032	0.006
60	0.22	0.014
61	0.293	0.04
62	0.2	0.02

Proposed use in the treatments of disorders

A local injection of apamin, which acts at the same K^+ channel and in the same way as the compounds of the present invention, reduces spontaneous and evoked electrical activity in the muscle of patients with myotonic muscular dystrophy [Behrens, M I., Jalil, P., Serani, A., Vergara, F. and Alvarez, O. (1994). Possible role of apamin-sensitive K^+ channels on myotonic dystrophy. Muscle & nerve, 17: 1264 - 1270]. However, apamin's central neurotoxicity rules out its systemic use; the compounds of the present invention are likely to be more selective in their action in reducing the hyperexcitability associated with this condition.

The inventors have found that compounds of the present invention, by blocking SK_{Ca} channels, increase the amplitude of peristalsis in intestinal smooth muscle at unprecedently low concentrations for a low molecular weight synthetic compound. The EC_{50} values for Compound 24 and Compound 10 are 0.5 nM and 1 nM respectively, as tested on isolated rabbit jejunum. This shows that the compounds of the present invention may act as a novel prokinetic agent for the treatment of gastrointestinal dysmotilities.

The parenteral administration of very small doses of apamin has been shown to facilitate memory processes involved in task learning in mice [Messier, C., Mourre, C., Bontempi, B., Sif, J., Lazdunski. M. and Destrade, C. (1991). Effect of apamin, a toxin that inhibits Ca^{2+}-dependent K^+ channels, on learning and memory processes. Brain Research, 551: 332 - 336; Belcadi-Abbassi, W. and Destrade, C. (1995). Post-test apamin injection suppresses a Kamin-like effect following a learning session in mice. Neuroreport. 6: 1293-1296]. The compounds of the present invention are likely to exert the same action as apamin in the treatment of disorders of memory, but with greater selectivity.

Narcolepsy and associated disorders are associated with the premature onset of rapid-eye-movement (REM) sleep. Intraventricularly-administered apamin produces a dose-dependent reduction in REM sleep expression in rats [Benington, J., Woudenberg, M.C. and Heller, H.C. (1995). Apamin, a selective SK channel blocker, suppresses REM sleep without a compensatory rebound. Brain Research, 692: 86 - 92]. The compounds of the present invention are likely to exert the same action as apamin, but with greater selectivity.

It has been suggested that dequalinium and other

lipophilic cationic compounds are likely to have anticarcinoma activity [Weiss et. al., Proc. Natl. Acad. Sci. USA. 1987, 84, 5444-8. Gamboa-Vujicic et. al, J. Pharm. Sci. 1993, 82, 231. Helige et. al, Eur. J. Cancer, 1993, 29A, 124.] The compounds of the present invention are likely to exert similar action, but with greater selectivity.

The intracerebro-ventricular injection of apamin has been found to inhibit ethanol-induced narcosis in mice [Yamamoto, H.-A. and Harris, R. A. (1983). Calcium-dependent ^{86}Rb efflux and ethanol intoxication: studies of human red blood cells and rodent brain synaptosomes. Eur. J. Pharmacol. 88: 357 - 363] providing behavioural evidence for the importance of SK_{Ca} channels in alcohol-induced coma and raising the possibility that SK_{Ca} blockers could be of value in its treatment. The compounds of the present invention are likely to exert the same action as apamin, but with greater selectivity.

Dequalinium is commonly found as an antibacterial agent, particularly in throat lozenges and similar preparations. It is therefore expected that the compounds of the present invention would exhibit antibacterial properties and could be used in

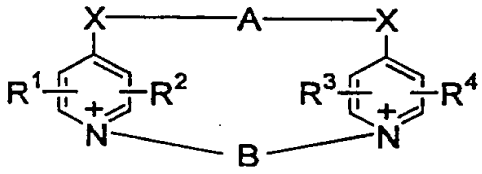
medicaments, e.g. throat lozenges, swabs, as such.

It is thought that the compounds of the present invention will exhibit selectivity between different types of SK_{Ca} channels. This may be due to some feature of the structure of the compounds of the present invention conferring the ability to discriminate between the different types of channel.

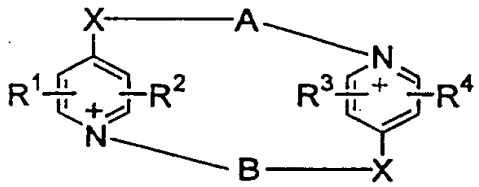
It should be understood that embodiments of the present invention have been described above by way of example only and various alternative modifications from what has been specifically described and illustrated can be made within the scope of the invention, as will be readily apparent to persons skilled in the art.

CLAIMS

1. A compound having the general formula I or II:



I

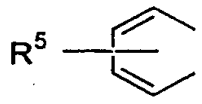


II

or any one of its conjugate bases

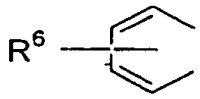
where:

each Q^- is the conjugate base of a pharmaceutically acceptable inorganic or organic acid;

R^1 is selected from H and 

R^5 being selected from H, and substituents such as a halogen, an alkyl group with 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an amino group, an alkylamino group, a hydroxy group and an alkoxy group;

R^2 and R^3 are independently selected from H, and substituents such as a halogen, an alkyl group with 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an amino group, an alkylamino group, a hydroxy group and an alkoxy group;

R^4 is selected from H and 

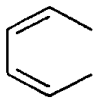
R^6 being selected from H, and substituents such as a halogen, an alkyl group with 1 to 10 carbon atoms, a haloalkyl group having 1 to 10 carbon atoms, an amino group, an alkylamino group, a hydroxy group and an alkoxy group;

where R^2, R^3, R^5 and R^6 may be present once or a plural number of times on the respective rings;

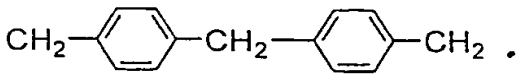
each X is independently selected from NH, NR^7, O, S and CH_2, R^7 being selected from alkyl, aryl, alkaryl and aralkyl groups having 1 to 10 carbon atoms;

A and B which are the same or different, are each selected from a spacing group with a chain length of 3 to 15 atoms;

except that in general formula I when

R^1 and R^4 are 

R^2 and R^3 are H, X is NH, and A is $(CH_2)_{10}$,

B cannot be  .

2. A compound according to claim 1 which has the general formula I and in which

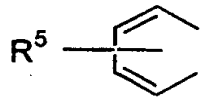
(i) each R^2, R^3, R^5 and R^6 is independently selected from H, a halogen, an alkyl group with 1 to 10

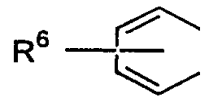
carbon atoms, an amino group, an alkylamino group, a hydroxy group and an alkoxy group, and

(ii) each X is selected from NH, O, S and CH_2.

3. A compound according to claim 1 or 2, wherein X is NH.

4. A compound according to claim 1, 2 or 3, wherein

R^1 and R^4 are 

and 

respectively.

5. A compound according to claim 4, wherein R^5 and R^6 are both H.

6. A compound according to claim 5, wherein R^2 and R^3 are both H.

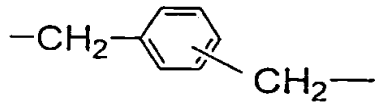
7. A compound according to any one of claims 1 to 6, wherein A and B are independently selected from:

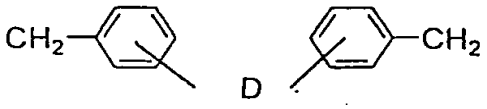
$-(CH_2)_n-$ where n=3-10;

$-(CH_2)_m-Z-(CH_2)_m$ wherein Z is O or S and each m is 1 to 5;

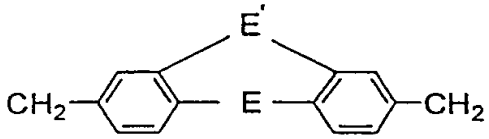
a straight chain alkene or alkyne containing one or two C=C or C≡C bonds respectively and having 3 to 10

carbon atoms;





where D is joined to the rings in the meta or para positions, and is selected from $(CH_2)_k$ where k=0-2, CH=CH, C≡C and a heterocyclic ring;



where E and E' are selected from $(CH_2)_k$ where k=0-2 and CH=CH; and

one or more of the aromatic rings in A and B may be substituted by one or more of the groups OH, alkoxy and halogen.

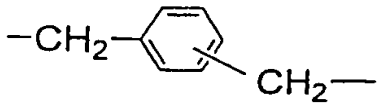
8. A compound according to claim 7, wherein A and B are independently selected from :

$-(CH_2)_n-$ where n=3-8;

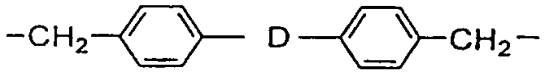
$-(CH_2)_m-Z-(CH_2)_m$ wherein Z is O or S and each m is 1 to 3;

a straight chain alkene or alkyne containing one or two C=C or C≡C bonds respectively and having 3 to 6

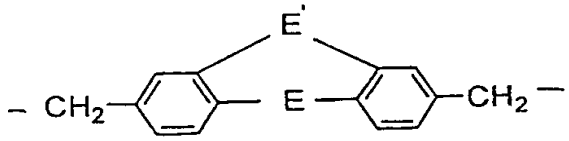
carbon atoms;



where the groups are meta or para to each other and where the ring is optionally substituted by one or more of the groups OH, methoxy and halogen;



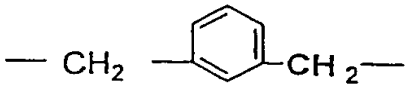
where D is selected from $(CH_2)_k$ where k=0 or 1, CH=CH, and a pyridine ring attached to the rings at the two sites ortho to the N atom; and



where E is CH_2 and E' is a direct link between the rings.

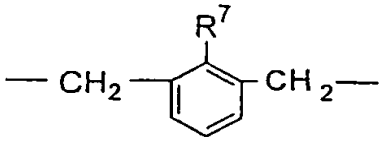
9. A compound according to claim 8, wherein A is selected from $-(CH_2)_n-$, where n=3-6,

and



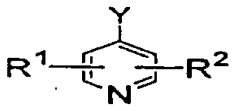
and B is selected from $-(CH_2)n$ where n=4-6,

and



where R^7 is selected from H, OH, OMe.

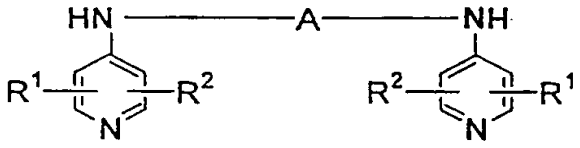
10. A method for producing a compound according to any one of claims 1 to 9 having the general formula I, by reacting a compound of the general formula:



with a compound of the formula

$$H_2N - A - NH_2$$

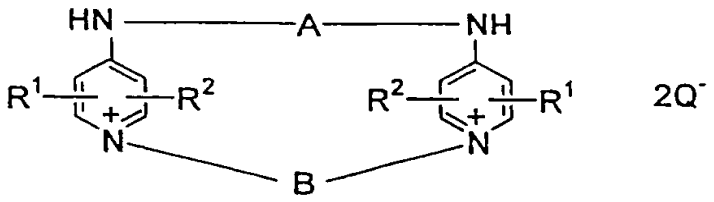
to give



which is then further reacted with a compound of the formula

$$Z - B - Z$$

to give

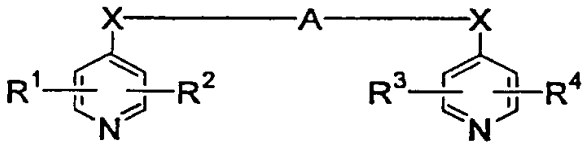


or any one of its conjugate bases,

where

Y and Z are independently selected from a sulphonate, Cl, Br and I.

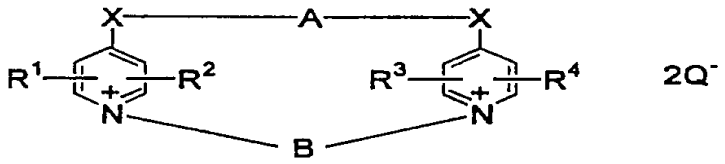
11. A method for producing a compound according to any one of claims 1 to 9 having the general formula I, by reacting a compound of the general formula



with a compound of the general formula

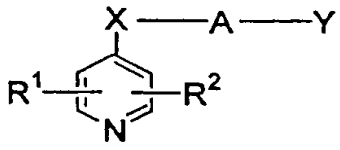
Z - B - Z

to give

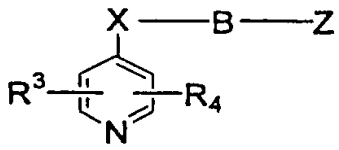


where Z is selected from Cl, Br and I.

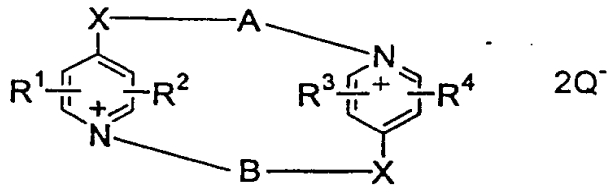
12. A method of producing a compound according to any one of claims 1 to 9 having the general formula II, by reacting a compound of the general formula III



with a compound of the general formula IV



to give



where Y and Z are independently selected from Cl, Br and I.

13. A method according to claim 12 wherein compounds III and IV are the same compound.

14. The use of a compound according to any one of claims 1 to 9 or Compound A in the treatment of myotonic muscular dystrophy, gastrointestinal dysmotility, a disorder of memory, narcolepsy or an associated disorder, a cancer, ethanol-induced neurotoxicity, or bacterial infection.

15. The use of a compound according to any one of claims 1 to 9 or Compound A in the preparation of a pharmaceutical for the treatment of myotonic muscular dystrophy, a gastrointestinal dysmotility, a disorder of memory, narcolepsy or an associated disorder, a cancer, or ethanol-induced neurotoxicity.

16. The use of a compound according to any one of claims 1 to 9 or Compound A in the preparation of an antibacterial agent.

17. A pharmaceutical composition containing a compound according to any one of claims 1 to 9 or Compound A.

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/GB 97/01659

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/18 C07D471/22 C07D515/18 C07D498/18 C07D513/18
A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 1 497 451 A (H.C. STARK) 13 October 1967 see column 1, line 1 - column 2, line 20; examples 1, 3-5,7,8; claims 1-2 ---	1-7,10, 11,14, 16,17
X	GB 895 090 A (H.C. STARK) 2 May 1962 see page 1, line 37 - page 2, line 22; example II ---	1,4,5, 7-9,11, 14,16,17
X	"DICTIONARY OF DRUGS, Chemical Data, Structures and Bibliographies" 1990 , CHAPMAN AND HALL SCIENTIFIC DATA DIVISION , LONDON, GB XP002043250 see page 159, entry B-00202 --- -/--	1-5,7, 14,16,17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1997	29. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/GB 97/01659

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 29 05 373 A (LABORATORI GAMBAR) 6 September 1979 see claims 1, 12, 16; page 7, paragraph 2; example 5a; page 13, lines 2-10; page 17 lines 7-11 and page 18, lines 12-15	1-5,7, 14,16,17
X	E. ALCALDE ET AL: CHEM. LETT., no. 10, 1995, pages 865-866, XP002043247 see page 865, scheme 1, compound 8	1,2,11
A	P.M. DUNN ET AL: BR. J. PHARMACOL., vol. 117, no. 1, 1996, pages 35-42, XP002043248 cited in the application see page 37, column 2, Drugs and reagents; pages 40-41, Discussion	1-7,10, 14,15,17
P,X	J. CAMPOS ROSA ET AL: BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 1, 7 January 1997, pages 7-10, XP002043249 see the whole document	1-7,10, 14,15,17

INTERNATIONAL SEARCH REPORT

*ernational application No
PCT/GB 97/01659

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1 [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2 [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1 [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4 [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claim 14
is directed to a method of treatment of the
human/animal body , the search has been carried out and based on the
alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern nal Application No
PCT/GB 97/01659

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 1497451 A	02-01-68	NONE	
GB 895090 A		NONE	
DE 2905373 A	06-09-79	FR 2418221 A	21-09-79